Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217188
Priority or standard	Priority
Submit date(s)	6/29/2022
Received date(s)	6/29/2022
PDUFA goal date	5/28/2023
Division/office	Division of Antivirals (DAV)
Review completion date	5/24/2023
Established/proper name	nirmatrelvir and ritonavir
(Proposed) proprietary name	PAXLOVID
Pharmacologic class	Nirmatrelvir: SARS-CoV-2 main protease (M^{pro}) inhibitor Ritonavir: HIV-1 protease inhibitor and CYP3A inhibitor
Other product name(s)	PF-07321322 (nirmatrelvir)
Applicant	Pfizer, Inc.
Dosage form(s)/formulation(s)	Co-packaged Tablets
Dosing regimen	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days
Applicant-proposed indication(s)/ population(s)	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death.
SNOMED CT code for proposed indication disease term(s)[1]	186747009 | Coronavirus infection (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days
Approved indication(s)/ population(s) (if applicable)	PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
SNOMED CT code for approved indication disease term(s)[1]	186747009 | Coronavirus infection (disorder)

[1] For internal tracking purposes only.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; HIV, human immunodeficiency virus; M^{pro}, main protease; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BLASTN	nucleotide basic local alignment search tool
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COVID	coronavirus disease
COVID-19	coronavirus disease 2019
CS	cleavage site
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug induced liver injury
E-DMC	external data monitoring committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
E-R	exposure-response
EUA	emergency use authorization
^{19}F-NMR	fluorine-19 nuclear magnetic resonance
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	FDA medical query
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
HIV-1	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
ICU	intensive care unit
IND	investigational new drug
ITT	intent-to-treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
MA	mouse adapted
MAD	multiple ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MHV	mouse hepatitis virus
mITT	modified intent-to-treat
M^{pro}	main protease
NCT	national clinical trial
NDA	new drug application
NGS	next-generation sequencing
NIH	National Institutes of Health
NIR	nirmatrelvir
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NP	nasopharyngeal
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamic
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	orally
PP	per-protocol
PT	prothrombin time
QSP	quantitative systems pharmacology
RT-PCR	real-time, reverse transcription-polymerase chain reaction
RWE	real-world evidence
SAE	serious adverse event
SAF	safety analysis set
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TEAE	treatment-emergent adverse event
TES	treatment-emergent substitution
ULN	upper limit of normal
VL	viral load

I. Executive Summary

1. Summary of Regulatory Action

This new drug application (NDA) for oral nirmatrelvir tablets co-packaged with ritonavir tablets (PAXLOVID) was submitted by Pfizer, Inc and was reviewed by the Food and Drug Administration (FDA) interdisciplinary team. Nirmatrelvir is a first-in-class peptidomimetic inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}). Ritonavir is a human immunodeficiency virus (HIV-1) protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. The intended indication for PAXLOVID is for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

The Applicant submitted an original investigational new drug (IND) in December 2020, for treatment of COVID-19; fast track designation was granted in February 2022. The FDA issued an emergency use authorization (EUA) for PAXLOVID on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19, including hospitalization and death.

This NDA received a priority review and was presented at the Antimicrobial Drugs Advisory Committee Meeting on March 16, 2023 to discuss whether the available data support a favorable benefit-risk assessment for the use of PAXLOVID for the intended indication. An overwhelming majority of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the proposed indication.

Each discipline (clinical, clinical virology, clinical pharmacology, pharmacology/toxicology, statistics, chemistry, and regulatory) did not identify any issues that preclude approval. I, the signatory authority for this application, concur with the approval recommendation. Please refer to the Approval Letter for further details.

The Applicant has conducted one pivotal clinical trial in adults who are at high risk for progression to severe COVID-19, EPIC-HR, to support the proposed indication. Additionally, data are available from two supporting clinical trials: EPIC-SR, which evaluated PAXLOVID for the treatment of mild-to-moderate COVID-19 in subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least one of the risk factors for progression to severe disease, and EPIC-PEP, which evaluated PAXLOVID used as post-exposure prophylaxis in adult household contacts of an individual with symptomatic COVID-19.

The PAXLOVID proposed dosage is 300 mg nirmatrelvir with ritonavir 100 mg orally (PO) twice daily for 5 days. The PAXLOVID 300 mg nirmatrelvir with ritonavir 100 mg twice daily for 5 days dosage was studied in the EPIC-HR, EPIC-SR, and EPIC-PEP clinical trials. EPIC-PEP also studied PAXLOVID for 10 days. In patients with moderate renal impairment (defined

as an estimated eGFR ≥30 to <60 mL/min), the proposed PAXLOVID dosage is 150 mg nirmatrelvir with 100 mg ritonavir PO twice daily for 5 days.

Pediatric patients 12 years of age and older weighing at least 40 kg were included in the EUA because the adult dosing regimen was anticipated to be appropriate for this population based on population pharmacokinetic (PK) modeling, and this met the distinct regulatory criteria for an EUA despite the lack of pediatric clinical data. However, to determine the optimal dose in the pediatric population, more data are needed from the ongoing clinical trial EPIC-PEDS, which is evaluating PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk pediatric subjects. (b) (4)

The available efficacy data from the clinical trials demonstrate that PAXLOVID is effective for its intended use. In the pivotal trial EPIC-HR in unvaccinated high-risk adults with mild-to-moderate COVID-19, PAXLOVID, when administered within 5 days of symptom onset, demonstrated a 5.6% absolute reduction and an 86% relative reduction, compared to placebo, for the primary endpoint of COVID-19 related hospitalization of or death from any cause through Day 28. Additional nonclinical, clinical, and clinical virology data analyses support that PAXLOVID continues to reduce the risk of COVID-19 related hospitalization or death from any cause through Day 28 in high-risk adults with mild-to-moderate COVID-19 regardless of baseline SARS-CoV-2 immunity or the infecting SARS-CoV-2 variant. The available safety data from the clinical trials demonstrate that PAXLOVID is safe for its intended use. I concur that the risks identified in the review of the clinical trial data can be mitigated through labeling and further evaluated during routine pharmacovigilance. The key safety concern with PAXLOVID is the risk of serious adverse reactions due to drug-drug interactions (DDIs) which will be described appropriately in labeling. A Boxed Warning has been included to ensure that prescribers are aware of this important risk.

Based upon review of all available efficacy and safety data, the benefits of PAXLOVID outweigh the risks for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. The availability of PAXLOVID will provide a new, effective, and convenient outpatient COVID-19 treatment option for this patient population. For detailed information supporting the basis for the benefit-risk assessment please refer to the details in this Integrated Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• COVID-19 is the disease caused by infection with SARS-CoV-2. Disease severity ranges widely, from mild to critical illness, and SARS-CoV-2 can also cause asymptomatic infection. • From when SARS-CoV-2 was first identified in late 2019 through April 2023, the CDC estimates there have been over 104 million COVID-19 cases and over 1.1 million COVID-19 deaths in the United States (CDC 2023a). While the weekly incidence of both COVID-19 cases and deaths have decreased substantially from their prior peaks of approximately 5.5 million cases and 23,000 deaths (from January 2022 and January 2021, respectively), there were still an average of 162,000 cases and 2,000 deaths per week in March 2023. • Risk factors for progression to severe COVID-19, including hospitalization and death, include age (with substantially increased risk at ages >65 years) and presence of one or more of certain underlying medical conditions (e.g., obesity, immunosuppressive conditions, chronic lung disease, cardiovascular disease, diabetes, cancer, chronic kidney disease, pregnancy). • COVID-19 vaccination status, and immunity from prior SARS-CoV-2 infection, also impact the risk for progression to severe COVID-19. • Circulating SARS-CoV-2 variants and subvariants have continously evolved, and the specific SARS-CoV-2 variant or subvariant can impact disease severity as well as the protection conferred by prior COVID-19 vaccination and/or prior SARS-CoV-2 infection.	• COVID-19 is a serious and potentially life-threatening illness which can result in pneumonia, respiratory failure, multiorgan failure, and death. While the incidence of COVID-19 cases and COVID-19-associated deaths have decreased substantially since earlier in the pandemic, likely in relation to increased population immunity from COVID-19 vaccination or prior infection, there were still an average of approximately 162,000 COVID-19 cases and 2,000 COVID-19-associated deaths per week in the United States in March 2023.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Remdesivir, administered by intravenous infusion daily for 3 days, is the only FDA-approved therapy currently available for the treatment of mild-to-moderate COVID-19 in individuals who are at high risk for progression to severe disease. – It may be logistically challenging for individuals with mild-to-moderate COVID-19 to find an accessible infusion center or other facility that can administer an intravenous infusion daily for 3 days, particularly as remdesivir treatment should be initiated within 7 days of symptom onset. • Two additional products are currently authorized under an EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease, though neither of these products are FDA-approved. These two products are the oral drugs PAXLOVID (the product being evaluated in this NDA application) and molnupiravir. The National Institutes of Health guidelines panel currently recommends only using molnupiravir when PAXLOVID and remdesivir are not available, feasible to use, or clinically appropriate (NIH 2022c). • Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) were previously available under EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease. However, no anti-SARS-CoV-2 mAbs are currently authorized for emergency use for COVID-19 treatment because of nonsusceptibility to the currently circulating SARS-CoV-2 Omicron subvariants.	• There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.
Benefit	• The efficacy of PAXLOVID was assessed in three Phase 2/3 clinical trials. – The pivotal trial, EPIC-HR, was a randomized, double-blind, global trial in which non-hospitalized adults who were unvaccinated for COVID-19 and at high risk for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. ▪ Treatment with PAXLOVID demonstrated a 5.6% (95% CI: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72%, 93%) relative reduction, compared to placebo, for the primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population (subjects who were dosed within 5 days of symptom onset and who at baseline did not receive nor were expected to receive COVID-19 therapuetic mAb treatment).	• Approval of PAXLOVID would provide an effective oral treatment option for mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. – PAXLOVID demonstrated overwhelming efficacy in EPIC-HR (p<0.0001) in reducing COVID-19 related hospitalization or death from any cause in unvaccinated adults with mild-to-moderate COVID-19. – While pre-existing SARS-CoV-2 immunity, either from vaccination or prior infection, is among the factors that impact the risk of progression to severe COVID-19, EPIC-HR and EPIC-SR clinical trial results support the efficacy of PAXLOVID for

	▪ Similar trends for the COVID-19 related hospitalization and death endpoint were observed across subject subgroups. ▪ Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)]. – EPIC-SR was a randomized, double-blind, global trial in which non-hospitalized adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. ▪ The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of time to sustained symptom alleviation through Day 28. ▪ However, a numerically lower rate of COVID-19 related hospitalizations or deaths from any cause through Day 28 was observed in all randomized subjects and in the subgroup of vaccinated high-risk subjects. – EPIC-PEP was a randomized, double-blind, global trial in which adult household contacts of individuals with symptomatic COVID-19 were randomized to receive 10 days of PAXLOVID, 5 days of PAXLOVID followed by 5 days of placebo, or 10 days of placebo for the post-exposure prophylaxis of COVID-19. ▪ The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of symptomatic SARS-CoV-2 infection through Day 14. • COVID-19 has evolved since the beginning of the COVID-19 pandemic and when the PAXLOVID registrational clinical trials were conducted. Currently in the United States: – The vast majority (>90%) of adults have either received one or more COVID-19 vaccine doses or have previously been infected with SARS-CoV-2. ▪ Although EPIC-HR enrolled unvaccinated adults with no prior confirmed SARS-CoV-2 infection, EPIC-HR and EPIC-SR subgroup analyses indicate that the relative risk reduction with PAXLOVID	the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. – Although clinical trial data to assess clinical efficacy against the SARS-CoV-2 Omicron variant are limited, based on the available virology data, it is reasonable to conclude that PAXLOVID is likely to retain clinical efficacy in adults with COVID-19 caused by currently circulating SARS-CoV-2 Omicron subvariants, and who are at high risk of progression to severe disease. – Comprehensive analyses conducted by FDA and the Applicant did not identify a clear association between PAXLOVID treatment and COVID-19 rebound. • More data are needed to determine if a longer duration of PAXLOVID dosing may be optimal for the treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised. • Additional clinical data are needed in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals in order to determine the appropriate dose and to make an assessment of benefit-risk in these individuals.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	versus placebo for COVID-19 related hospitalization or death from any cause is similar (>50%) in high-risk subjects regardless of prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus. – The Omicron variant is responsible for essentially all SARS-CoV-2 infections. ▪ Clinical trial data to directly determine the clinical efficacy of PAXLOVID in high-risk adults infected with the Omicron variant are limited. • In EPIC-HR, ~99% of subjects were infected with the Delta variant and the Omicron variant was not observed. • In the first half of EPIC-SR (2021), 98% of subjects were infected with the SARS-CoV-2 Delta variant. In the second half of EPIC-SR (2022), 100% of subjects were infected with the SARS-CoV-2 Omicron variant (mostly BA.2 and BA.2.12.1), but high-risk subjects were not enrolled during this time period due to the availability of PAXLOVID through the EUA. ▪ Analyses of nonclinical and clinical virology data demonstrate that PAXLOVID retains antiviral activity against the Omicron variant and major subvariants. In addition, bioinformatics analysis demonstrate that the PAXLOVID target (the SARS-CoV-2 main protease) is highly conserved across SARS-CoV-2 variants. – Different clinical presentations of COVID-19 have become more well known, including persistent SARS-CoV-2 infection in severely immunocompromised individuals and COVID-19 rebound, which is characterized by a relapse of symptoms or SARS-CoV-2 detection after initial recovery. ▪ Less than one percent of subjects in EPIC-HR were classified as having immunosuppression. ▪ In comprehensive post hoc analyses of clinical trial data conducted by FDA and the Applicant, viral RNA rebound and symptom rebound were observed in both PAXLOVID and placebo recipients, and at frequencies that were generally similar in both arms across multiple analyses. • Clinical trials are ongoing in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Clinical trial safety data are available from over 2400 subjects who received the proposed PAXLOVID dosing regimen (nirmatrelvir 300 mg and ritonavir 100 mg both twice daily for 5 days), plus over 900 subjects who received PAXLOVID for 10 days in EPIC-PEP. • In addition, over 11 million patients worldwide have received PAXLOVID for the treatment of COVID-19 since it was first authorized for emergency use in December 2021, and post-authorization safety reports of AEs after PAXLOVID use were reviewed to detect safety signals outside of the clinical trial setting. • PAXLOVID demonstrated an overall favorable safety profile in the clinical trials. The incidences of AEs were generally similar between treatment groups in EPIC-HR, EPIC-SR, and EPIC-PEP. The incidences of severe AEs, serious AEs, and AEs leading to permanent discontinuation of study drug were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in PAXLOVID-treated subjects. • The most common EPIC-HR treatment-emergent AEs (≥2% incidence) in the PAXLOVID group in the clinical trials were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group (4.6% and 3.0% versus 0.1% and 1.5%, respectively). These AEs were generally mild in severity. • The most common treatment-emergent AEs observed in EPIC-SR and EPIC-PEP were consistent with those observed in EPIC HR. • In the EPIC-PEP trial, similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups. • Prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID. • Based on post-authorization safety reports, the following additional adverse reactions have been identified with PAXLOVID use: anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise. • The key safety concern related to PAXLOVID use is the risk of serious adverse reactions due to DDIs, mainly related to the ritonavir component (ritonavir is a potent CYP3A inhibitor).	• PAXLOVID has an acceptable safety profile for the indicated patient population. • The major adverse reactions identified in the clinical trials were dysgeusia and diarrhea. • The key safety concern with PAXLOVID is the risk of serious adverse reactions due to DDIs: prescribers need to review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. In addition, prescribers need to consider the benefit of PAXLOVID treatment in reducing hospitalization and death versus the risk of potential DDIs for an individual patient. The risk of DDIs will be described appropriately in labeling, including a Boxed Warning to ensure that prescribers are aware of this important risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Because EPIC-HR, EPIC-SR, and EPIC-PEP excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious AEs, this risk cannot be evaluated through analysis of these clinical trial data. – Based on analyses of post-authorization use of PAXLOVID: ▪ Over 50% of PAXLOVID-eligible patients are on medications with DDIs with PAXLOVID (though the most common medications with DDIs could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring). ▪ The majority of PAXLOVID prescribers are adult primary care practitioners (who may not be experienced in managing ritonavir DDIs). ▪ Serious adverse reactions, including death, have been reported in association with DDIs that are included in the current EUA Fact Sheet for Healthcare Providers. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.	

Abbreviations: AE, adverse event; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP3A, cytochrome P450, family 3, subfamily A; DDI, drug-drug interaction; EUA, emergency use authorization; FDA, Food and Drug Administration; mITT, modified intent to treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U.S., United States

2.2. Conclusions Regarding Benefit-Risk

COVID-19 is a serious and potentially life-threatening illness that has led to over one million deaths in the United States since SARS-CoV-2, the causative virus, was first identified in late 2019. While the weekly incidence of COVID-19 cases as well as of COVID-19 related deaths have decreased substantially from their peaks due to increased population immunity from COVID-19 vaccines and prior SARS-CoV-2 infection, approximately two thousand COVID-19 related deaths were still reported in the United States each week in March 2023. Currently, the only approved treatment option for outpatients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease is remdesivir, which must be administered by IV infusion daily for three days. Additional effective, convenient, outpatient COVID-19 treatment options are needed.

PAXLOVID, an orally administered antiviral product, has clearly demonstrated clinical benefit for high-risk adults with mild-to-moderate COVID-19. In the pivotal trial EPIC-HR in unvaccinated high-risk adults with mild-to-moderate COVID-19, PAXLOVID, when administered within 5 days of symptom onset, demonstrated a 5.6% absolute reduction and an 86% relative reduction, compared to placebo, for the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. This risk reduction was highly statistically significant and was consistent across subgroups. While the COVID-19 pandemic has evolved since the conduct of EPIC-HR, with most adults now having some baseline SARS-CoV-2 immunity from vaccination or prior infection and with evolving SARS-CoV-2 variants, available data continue to support that PAXLOVID reduces the risk of COVID-19 related hospitalization or death from any cause through Day 28 in high-risk adults with mild-to-moderate COVID-19 regardless of baseline SARS-CoV-2 immunity or the infecting SARS-CoV-2 variant. Furthermore, comprehensive analyses did not identify an association between PAXLOVID treatment and COVID-19 rebound, a concern that was raised with use of PAXLOVID under emergency authorization.

The safety database for PAXLOVID is adequate for the proposed indication, dosing regimen, and population. Overall, PAXLOVID has a favorable safety profile: adverse reactions associated with PAXLOVID use identified in clinical trials were dysgeusia and diarrhea, which were generally infrequent and mild in severity. The key safety concern with PAXLOVID relates to the risk of serious adverse reactions due to drug-drug interactions (DDIs), mainly related to the ritonavir component (ritonavir is a potent CYP3A inhibitor). The risk of DDIs will be described appropriately in labeling, including a Boxed Warning to ensure that prescribers are aware of this important risk.

The overall benefit-risk profile for PAXLOVID is favorable to support an indication for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease. Areas of uncertainty include if a longer duration of PAXLOVID dosing may be optimal for the treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised, along with the appropriate dose and data to inform benefit-risk assessment in pediatric individuals, individuals with severe renal impairment, pregnant individuals, and lactating individuals. In our decision to approve PAXLOVID, we considered the available safety and efficacy data, the recommendation for approval by all review disciplines, and the Antimicrobial Drugs Advisory Committee vote where the majority (94%) of the

committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The availability of PAXLOVID will provide a new, effective, and convenient outpatient COVID-19 treatment option for this patient population.

II. Interdisciplinary Assessment

3. Introduction

Background of the Condition/Standard of Clinical Care

Coronavirus disease 2019 (COVID-19) is a serious and potentially life-threatening illness which can result in pneumonia, multiorgan failure, respiratory failure, and death. Through April 7, 2023, the Centers for Disease Control and Prevention (CDC) estimates there have been over 104 million COVID-19 cases and over 1.1 million COVID-19 deaths in the United States. While the weekly incidence of both COVID-19 cases and deaths have decreased substantially from their prior peaks of approximately 5.5 million cases and 23,000 deaths (from January 2022 and January 2021, respectively), there were still an average of approximately 162,000 cases and 2,000 deaths per week in March 2023 (CDC 2023a). Patients with COVID-19 can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe illness is defined as an oxygen saturation <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mmHg, a respiratory rate >30 breaths/minute, or lung infiltrates >50%. Critical illness is defined as individuals who have respiratory failure, septic shock, and/or multiorgan dysfunction (May 2020; NIH 2022a).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged over time and continue to emerge. By late January 2022, it was estimated that the Omicron variant was responsible for more than 99% of SARS-CoV-2 infections in the United States (Lambrou et al. 2022). The Omicron variant and its numerous subvariants have been noted to have substantial evasion of neutralizing antibodies (Willett et al. 2022) and may be more transmissible when compared with previous variants of concern (Baker et al. 2022); however, the risk of severe disease or death may be lower (Adjei et al. 2022).

To date, remdesivir is the only Food and Drug Administration (FDA) approved therapy for the treatment of mild-to-moderate COVID-19 in non-hospitalized adults who are at high risk for progression to severe disease (Gilead Sciences 2020). Remdesivir, administered by intravenous infusion for 3 days, is a nucleotide prodrug of an adenosine analog and binds to the viral RNA-dependent RNA polymerase/template complex and inhibits viral replication by terminating RNA transcription prematurely (NIH 2022d). Remdesivir retains antiviral activity in cell-based assays against the Omicron variant and its subvariants (NIH 2022d).

In December 2021, the FDA issued an emergency use authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate. Molnupiravir is the oral prodrug of N4-hydroxycytidine, a ribonucleoside which, after phosphorylation to the active triphosphate, incorporates into viral RNA by viral RNA-dependent RNA-polymerases resulting in an accumulation of errors in the viral genome leading to inhibition of replication (known as viral

error catastrophe or viral lethal mutagenesis) (NIH 2022c).The National Institutes of Health guidelines panel currently recommends only using molnupiravir when PAXLOVID and remdesivir are not available, feasible to use, or clinically appropriate (NIH 2022c).

Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) have previously shown clinical benefit in treating COVID-19; however, laboratory studies have found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants can vary dramatically (NIH 2022b). By the end of January 2023, FDA had made determinations, based on the terms and conditions of each respective EUA, that have resulted in all of the mAb therapies not being authorized in the United States until further notice by the Agency. FDA made such determinations based on the variant susceptibility to the particular therapeutic and CDC variant frequency data.

Pertinent Drug Development and Regulatory History

PAXLOVID is oral nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}). Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing polyprotein precursors, preventing viral replication. Ritonavir is a human immunodeficiency virus (HIV-1) protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The Applicant has submitted a new drug application (NDA) seeking approval of PAXLOVID for the proposed indication of treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The PAXLOVID proposed dosage is 300 mg nirmatrelvir with ritonavir 100 mg orally (PO) twice daily (BID) for 5 days. In patients with moderate renal impairment (defined as an eGFR ≥30 to <60 mL/min), the proposed PAXLOVID dosage is 150 mg nirmatrelvir with 100 mg ritonavir PO twice daily for 5 days.

To support the proposed indication, the Applicant has conducted one pivotal clinical trial in adults who are at high risk for progression to severe COVID-19, EPIC-HR, to support the proposed indication. Additionally, data are available from two supporting clinical trials: EPIC-SR, which evaluated PAXLOVID for the treatment of mild-to-moderate COVID-19 in subjects who were either fully vaccinated or who had no risk factors for progression to severe COVID-19, and EPIC-PEP, which evaluated PAXLOVID used as post-exposure prophylaxis in adult household contacts of an individual with symptomatic COVID-19.

The Applicant previously submitted an original investigational new drug (IND) in December 2020, for treatment of COVID-19, fast track designation was granted in February 2022. The FDA issued an EUA for PAXLOVID on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19, including hospitalization and death. The EUA dosing regimen was primarily supported by adult interim data from EPIC-HR, in which PAXLOVID was generally safe and well-tolerated and reduced the risk of COVID-19 related hospitalization or death from any cause through Day 28. Please refer to Section 12 for complete regulatory history.

- Pediatric patients 12 years of age and older weighing at least 40 kg were included in the EUA because the adult dosing regimen was anticipated to be appropriate for this population based

on population pharmacokinetic (PK) modeling, and this met the distinct regulatory criteria for an EUA despite the lack of pediatric clinical data. However, to determine the optimal dose in the pediatric population, more data are needed from the ongoing clinical trial EPIC-PEDS, which is evaluating PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk pediatric subjects.

This NDA was given priority review; the Prescription Drug User Fee Act (PDUFA) goal date was extended by three months due to a major amendment based on submissions received on November 23 and December 5, 2022. These submissions contained extensive key efficacy, safety, and virology reanalyses following removal of select clinical trial sites due to data reliability and good clinical practice (GCP) noncompliance issues (see Section 6.3.1).

An Advisory Committee meeting was held on March 16, 2023 to discuss whether the available data support a favorable benefit-risk assessment for the use of PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. A majority (94%) of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the proposed indication. Please refer to Section 11 for further Advisory Committee meeting information.

The review team identified several key review issues that had a significant impact on the overall regulatory assessment of PAXLOVID as outlined in Section 3.1. In-depth analyses of these efficacy and safety review issues can be found in Section 6.3 and Section 7.7 respectively.

3.1. Review Issue List

The review team identified seven key review issues relevant to the evaluation of benefit (Section 6.3) and one key review issue relevant to the evaluation of risk (Section 7.7).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Data Reliability Issues at Specific Clinical Trial Sites

- The review team identified unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects enrolled at selected study sites in EPIC-HR and EPIC-SR. These observations triggered additional site inspections and in-depth investigations of all study data and sites from EPIC-HR and EPIC-SR to determine if there were data reliability issues.

3.1.1.2. Efficacy in High-Risk Adults Who Are Vaccinated Against COVID-19 or Previously Infected With SARS-CoV-2

- The pivotal trial, EPIC-HR, only enrolled subjects without prior SARS-CoV-2 vaccination and without prior confirmed SARS-CoV-2 infection.
- Currently, an overwhelming majority of the U.S. population has either received one or more COVID-19 vaccine doses, or previously been infected with SARS-CoV-2.

3.1.1.3. Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

- The clinical trial data from EPIC-HR and from EPIC-SR (through the December 19, 2021 data cutoff) were from a time before the emergence of the SARS-CoV-2 Omicron variant, which currently accounts for essentially all SARS-CoV-2 infections in the United States.

3.1.1.4. Efficacy in High-Risk Patients With Mild Disease

- EPIC-HR and EPIC-SR enrolled subjects with mild to moderate COVID-19, but per the protocols subjects were not further classified as to whether their COVID-19 was mild versus moderate.
- Since the EUA of PAXLOVID in December 2021, there have been several articles questioning whether PAXLOVID should be taken by patients who are only mildly ill.

3.1.1.5. Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

- The Phase 3 treatment trials evaluated a 5-day duration of PAXLOVID treatment, but less than 1 percent of subjects enrolled in EPIC-HR were classified as having immunosuppression.
- Individuals with moderate to severe immunosuppression may take longer than the general population to clear SARS-CoV-2 infection in the absence of treatment, and persistent SARS-CoV-2 infection has been reported in immunocompromised patients.

3.1.1.6. Impact of PAXLOVID on COVID-19 Rebound

- COVID-19 rebound, defined as recurrence of symptoms and/or SARS-CoV-2 RNA detection in upper respiratory tract samples after initial resolution, has been reported in patients after completion of PAXLOVID treatment. Analyses of the EPIC-HR and EPIC-SR data were conducted to assess whether COVID-19 rebound is associated with PAXLOVID use or whether COVID-19 rebound simply reflects the natural history of SARS-CoV-2 infection.

3.1.1.7. Benefit of PAXLOVID for the Prevention of Post-COVID Conditions

- Post- coronavirus disease (COVID) conditions, or long COVID, have been described after resolution of the acute SARS-CoV-2 infection.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Serious Adverse Reactions Due to Drug-Drug Interactions (DDIs)

- PAXLOVID contains ritonavir, a potent CYP3A inhibitor, that can result in significant elevations of concomitant medications that are metabolized by the CYP3A isoenzyme.
- EPIC-HR and EPIC-SR excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious adverse reactions.
- Data from the use of PAXLOVID under EUA were evaluated to assess the risk of serious adverse reactions due to DDIs.

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials conducted to support the benefit-risk assessment of PAXLOVID. Data from the Phase 2/3 trial EPIC-HR provide the primary basis of efficacy and safety of PAXLOVID for treatment in patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Results from the Phase 2/3 trials EPIC-SR (non-hospitalized adults with mild-to-moderate COVID-19 who were either unvaccinated with no risk factors for progression to severe disease or were vaccinated against COVID-19 and at high risk for severe disease) and EPIC-PEP (prevention of symptomatic SARS-CoV-2 infection in adult household contacts of individuals with COVID-19) provide supportive safety and efficacy data.

Phase 1 trials, data from the Safety Update Report, and post-authorization reports of adverse events (AEs) after PAXLOVID use under the EUA were also reviewed to provide additional safety experience.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for PAXLOVID

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-HR (C4671005) [NCT04960202]	Non-hospitalized symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness.	Control type: PC Randomization: Randomized 1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours (N=1038); placebo (N=1053) Number treated: 2091 Duration: 5 days	Primary: • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 symptom onset. Key Secondary: • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 symptom onset. • Time to sustained alleviation of in all targeted signs/symptoms through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 symptom onset.	Planned:3000 Actual: 2113	Centers: 189 Countries: 19

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-SR (C4671002) [NCT0501151]	Adult outpatients with COVID-19 who are fully vaccinated and have at least one risk factor for progression to severe disease or who are unvaccinated and have no risk factors for progression to severe disease.	Control type: PC Randomization: Randomized 1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours (N=540); placebo (N=528) Number treated: 1068 Duration: 5 days	Primary: • Time to sustained alleviation of all COVID-19 signs/symptoms through Day 28 in all subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and were dosed within ≤3 days of COVID-19 symptom onset. Key Secondary: • Time to sustained alleviation of all COVID-19 signs/symptoms through Day 28 in all subjects randomly assigned to study intervention who took at least 1 dose of study intervention. • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in all subjects randomly assigned to study intervention who took at least 1 dose of study intervention.	Planned:1140 (extended to 1980 for 2022 enrollment) Actual: 1075 (data cutoff December 19, 2021)	Centers: 171 Countries: 16

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen[2] (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[3]	Number of Centers and Countries[3]
EPIC-PEP (C4671006) [NCT05047601]	Asymptomatic adults with a negative screening SARS-CoV-2 rapid antigen test and who were exposed to household contacts who were symptomatic with confirmed COVID-19	Control type: PC Randomization: Randomized 1:1:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug: PAXLOVID (300 mg nirmatrelvir/ 100 mg ritonavir) administered orally Dosage: PAXLOVID every 12 hours, 5 days (N=912); PAXLOVID every 12 hours, 10 days (N=911); placebo (N=898) Number treated: 2721 Duration: 5 or 10 days	Primary: • Proportion of subjects who develop a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 among subjects who have a negative RT-PCR result at baseline. Key Secondary: • The proportion of subjects with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adult subjects who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19.	Planned:2880 Actual: 2736	Centers:147 Countries:17

Source: Clinical study report and adsl.xpt for each trial.
[1.] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2.] Number of subjects treated based on the safety population
[3.] Based on the full analysis set, excluding subjects from sites with data reliability issues
Abbreviations: BID, twice daily; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; DB, double-blind; LTE, long-term extension; MC, multicenter; N, number of subjects in treatment group; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; h, hour; d, day; wk, week(s); mo, month(s); y, year(s)

4. Patient Experience Data

The protocol included collection of patient-reported outcomes using three instruments to measure the impact of PAXLOVID: Global Impression Questions, Work Productivity and Activity Impairment Questionnaire, and Euroquol Quality of Life 5-Dimension 3-Level Scale. However, these data were not submitted. The Applicant also captured symptom data in the clinical trials.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	• EPIC-HR: Symptom Diary related efficacy endpoints (Section 6.2.1.3) • EPIC-SR: Primary efficacy endpoint (Section 6.2.2.3) • Review issues: COVID-19 rebound (Section 6.3.6), post-COVID conditions (Section 6.3.7)
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Mechanism of Action

- Nirmatrelvir (NIR) is an oral peptidomimetic inhibitor of the SARS-CoV-2 M^{pro}, also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5). NIR inhibits M^{pro} by binding directly to the M^{pro} active site, forming a covalent bond with the catalytic residue (C145) and non-covalent interactions with ten other residues. M^{pro} inhibition prevents proteolytic processing of the viral polyproteins pp1a/pp1ab, a critical early step in the viral replication cycle. The mechanism of action of nirmatrelvir as a SARS-CoV-2 M^{pro} inhibitor is supported by data from biochemical, cell culture, and animal studies.

Summary of Data Reviewed for Nonclinical Virology-Related Studies

- Key results and conclusions from nonclinical virology-related studies are summarized in the following text. Additional details are provided in Sections 18 and 20.

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro} enzyme with an IC_{50} value of 19.2 nM and a K_i value of 3.1 nM. Nirmatrelvir also inhibited recombinant M^{pro} enzymes from other human coronaviruses (SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63), with IC_{50} values ranging from 28.9 to 479 nM.
- Using X-ray crystallography, nirmatrelvir was shown to bind directly to the active site of recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro}. In the cocrystal structure, nirmatrelvir was covalently bound to the catalytic amino acid residue C145 and formed non-covalent interactions with ten other residues: H41, M49, F140, G143, H163, H164, M165, E166, L167, and P168. Twelve additional residues were located within 5 Å but did not directly contact nirmatrelvir: Y54, L141, N142, S144, H172, V186, D187, R188, Q189, T190, A191, and Q192.
- The 23 SARS-CoV-2 M^{pro} residues that directly interacted with nirmatrelvir or were located in close proximity (<5 Å) of nirmatrelvir were found to be highly conserved in the GISAID EpiCov sequence database (~12.7 million sequences; accessed November 30, 2022), with polymorphism frequencies ≤0.1%.
- In cell culture, nirmatrelvir had activity against SARS-CoV-2 in differentiated normal human bronchial epithelial (dNHBE, EC_{50} value: 32.6-61.8 nM [16.3-30.9 ng/mL]), A549-ACE2 (EC_{50} value: 77.9 nM), and Vero E6 (EC_{50} value: 4,480 nM) cells. Nirmatrelvir activity was weaker in Vero E6 cells due to high levels of P-glycoprotein (P-gp) expression in this cell line. In the presence of a P-gp inhibitor (CP-100356), nirmatrelvir had a ~60-fold lower EC_{50} value of 74.5 nM in Vero E6 cells, comparable to the EC_{50} values observed in other cell

types. The lower level of P-gp expression in A549-ACE2 and dNHBE cells, which are both of respiratory tissue origin, is considered more relevant and predictive of P-gp expression in key tissue sites of SARS-CoV-2 infection, relative to Vero E6 cells (African green monkey kidney cell line).

- Nirmatrelvir retained activity (≤3-fold change in EC_{50} value relative to WA1/2020) against 15 SARS-CoV-2 variants in cell culture: Alpha/B.1.1.7, Gamma/P.1, Delta/B.1.617.2, Lambda/C.37, Mu/B.1.621, and Omicron BA.1, BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5. Nirmatrelvir had reduced activity (3.0-4.4-fold change in EC_{50} value) against Beta/B.1.351 in some assays but not in other assays. These experiments were performed in Vero E6 P-gp knockout cells, Vero E6-TMPRSS2 cells treated with a P-gp inhibitor, or HeLa-ACE2 cells.
- Nirmatrelvir also had activity against SARS-CoV-1 in Vero E6 cells (EC_{50} value: 151 nM with a P-gp inhibitor), MERS-CoV in Vero 81 cells (EC_{50} value: 166 nM with a P-gp inhibitor), and HCoV-229E in MRC-5 cells (EC_{50} value: 190 nM). Thus, nirmatrelvir appears to have broad anti-CoV activity. Nirmatrelvir did not have activity against enterovirus 71 or human rhinovirus 1B, which encode 3C proteases structurally related to M^{pro}. These results indicate that the antiviral activity of nirmatrelvir is likely restricted to coronaviruses.
- Ritonavir, an HIV-1 protease inhibitor and pharmacokinetic enhancer, did not have activity against SARS-CoV-2 in cell culture (tested up to 3,000 nM). In addition, ritonavir did not significantly antagonize the activity of nirmatrelvir against SARS-CoV-2 in cell culture.
- Nirmatrelvir was 69%, 57%, or 52% bound to plasma protein from humans, cynomolgus monkeys, or rats, respectively, across a range of drug concentrations, as measured by equilibrium dialysis. The Applicant selected a nirmatrelvir target plasma exposure (C_{min}) of 585 nM (292 ng/mL) for clinical studies, which is equivalent to the unbound EC_{90} value against SARS-CoV-2 in dNHBE cells (181 nM [90 ng/mL]).

Assessments of Cytotoxicity and Off-Target Activity

- Nirmatrelvir had low cytotoxicity in A549-ACE2 (CC_{50} value >3 μM), Vero E6 (CC_{50} value >100 μM with or without a P-gp inhibitor), Vero 81 (CC_{50} value >100 μM with a P-gp inhibitor), and MRC-5 (CC_{50} value >100 μM) cells used in antiviral activity studies, with favorable selectivity indices (CC_{50} values/EC_{50} values) against SARS-CoV-2 of >38.5 to >1,250 across different experiments.
- In biochemical assays, nirmatrelvir did not inhibit 8 mammalian proteases (IC_{50} values >100 μM or >10 μM), including 3 cysteine proteases. In addition, nirmatrelvir did not inhibit HIV-1 protease (IC_{50} value >100 μM). These results indicate that the activity of nirmatrelvir is selective for M^{pro}.

Resistance Development and Cross-Resistance

- In biochemical assays, nirmatrelvir activity against recombinant SARS-CoV-2 M^{pro} was significantly reduced (≥3-fold higher K_i value) by 19/101 of the single substitutions tested: Y54A (25-fold), F140A/L/S (7.6-260-fold), G143S (3.6-fold), S144A/E/T (46-480-fold), H164N (6.7-fold), E166A/G/V (6.2-7,700-fold), H172Y (250-fold), A173S/V (4.1-16-fold), R188G (38-fold), Q192L/P (6.8-29-fold), and V297A (3.0-fold). In addition, nirmatrelvir

activity was significantly reduced by 15/22 of the substitution combinations tested: T21I+L50F+A193P+S301P (7.3-fold), T21I+S144A (20-fold), T21I+S144A+T304I (51-fold), T21I+C160F+A173V+V186A+ T304I (28-fold), T21I+E166V (11,000-fold), T21I+A173V (15-fold), T21I+A173V+T304I (55-fold), L50F+F140L+L167F+T304I (190-fold), L50F+E166A+L167F (210-fold), L50F+E166V (4,500-fold), E55L+S144A (56-fold), T135I+T304I (5.1-fold), F140L+A173V (95-fold), H172Y+P252L (180-fold), and A173V+T304I (28-fold). In most of these combinations, the primary M^{pro} substitution(s) responsible for the reduced activity of nirmatrelvir appeared to be F140L, S144A, E166A/V, H172Y, and A173V.

- In cell culture, resistance selection experiments were first conducted with mouse hepatitis virus (MHV), a betacoronavirus used as a surrogate for SARS-CoV-2. Nirmatrelvir inhibited MHV replication in L929 cells with EC_{50} values of 847 and 395 nM in the absence and presence of P-gp inhibitor, respectively. The reduced activity of nirmatrelvir against MHV may be due to several amino acid differences near the nirmatrelvir binding site, including N142C, H164Q, M165L, P168S, V186R, R188A, T190V, and A191V. Nirmatrelvir-selected MHV acquired eight distinct M^{pro} substitutions: P15A, T50K, P55L, F126L, T129M, S144A, F213L, and A250V. The equivalent residues in SARS-CoV-2 are G15, L50, E55, Y126, A129, S144, I213, and P252, respectively. The MHV M^{pro} P55L and S144A substitutions were associated with reduced nirmatrelvir activity (4.4-4.9-fold higher EC_{50} values). SARS-CoV-2 M^{pro} substitutions at several of these positions have been associated with nirmatrelvir resistance in cell culture, including L50F, S144A, and P252L.
- In Vero E6 P-gp knockout cells, nirmatrelvir -selected SARS-CoV-2 (WA1/2020) acquired seven distinct M^{pro} substitutions: T21I, L50F, T135I, S144A, A173V, A191V, and T304I. The substitution frequencies indicate that some viruses had multiple M^{pro} substitutions, e.g., A173V+T304I, T21I+T304I, and T21I+S144A+T304I. Nirmatrelvir activity was significantly reduced (≥3-fold higher EC_{50} value) against six plaque-purified viruses with the following M^{pro} substitutions: T304I (3.4-fold), T21I+T304I (7.9-fold), L50F+T304I (5.9-fold), T135I+T304I (3.8-fold), A173V+T304I (20.2-fold), and T21I+S144A+T304I (27.8-fold).
- In A549-ACE2 cells, nirmatrelvir -selected SARS-CoV-2 (WA1/2020) acquired the M^{pro} F140L and A173V substitutions. Nirmatrelvir activity was significantly reduced (≥3-fold higher EC_{50} value) against plaque-purified virus with the F140L+A173V substitutions (10.1-fold) but not the A173V substitution alone (0.9-fold). Virus cultures with only the F140L substitution were not identified.
- In Vero E6 P-gp knockout cells or Vero E6-TMPRSS2 cells (with P-gp inhibitor), nirmatrelvir had reduced activity (EC_{50} value fold-change ≥3) against recombinant SARS-CoV-2 viruses with M^{pro} F140L (4.1), E166A (3.3), A173S (3.2), E55L+S144A (6.5), S144A+T304I (3.1), and T21I+A260V+T304I (3.2) substitutions. Nirmatrelvir retained activity (EC_{50} value fold-change <3) against recombinant viruses with M^{pro} G15S, E55L, L89F, K90R, S144A, H164N, E166G, Q189K, Q192L, T304I, and E166G+L232I substitutions. Recombinant viruses could not be generated with M^{pro} Y54A, F140A/I/S, S144E/L/P/T, E166V, H172Y, A173T, and A191V substitutions.
- Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro}

inhibitors). Nirmatrelvir is known to exhibit partial cross-resistance with some other M^{pro} inhibitors under development.

Activity in Animal Models of SARS-CoV-2 Infection

- Nirmatrelvir (±ritonavir) was shown to have antiviral activity against mouse-adapted (MA) SARS-CoV-2 MA10 in 129 and BALB/c mice. SARS-CoV-2 MA10 causes severe, and in some cases lethal, lung disease in mice, with the extent of lethality depending on infectious dose and age of the mice (Leist et al. 2020). SARS-CoV-2 MA10 does not encode any M^{pro} substitutions relative to SARS-CoV-2. These studies had several limitations. Nirmatrelvir dosing was initiated early and modeled post-exposure prophylaxis rather than treatment of symptomatic disease. In addition, the studies were terminated shortly after infection, such that the impact of nirmatrelvir on lethality was not assessed. Lastly, the utility of these animal models for predicting clinical outcomes is uncertain. However, these studies demonstrated a consistent antiviral effect and are further supportive of the antiviral activity of nirmatrelvir.
- In 129 mice, nirmatrelvir was administered PO at 300 or 1,000 mg/kg BID, beginning 4- or 12-hours post-infection on Day 0 and continuing through Day 2. Mice were euthanized on Day 3 for determination of lung virus titers and lung histopathology. At 1,000 mg/kg, nirmatrelvir prevented weight loss, reduced lung virus titers by ~4 $\log_{10}$, and reduced lung histopathology relative to vehicle-treated mice.
- In BALB/c mice, nirmatrelvir was administered PO at 300 or 1,000 mg/kg BID, beginning 4 hours post-infection on Day 0 and continuing through Day 3. Mice were euthanized on Day 4 for determination of lung virus titers, lung histopathology, and immunohistochemistry. Nirmatrelvir prevented weight loss, reduced lung virus titers by ~1.4 $\log_{10}$ (300 mg/kg) or ~1.9 $\log_{10}$ (1,000 mg/kg), reduced lung histopathology, and reduced SARS-CoV-2 nucleocapsid staining in the lungs relative to vehicle-treated mice.
- In BALB/c mice, nirmatrelvir (300 mg/kg BID), ritonavir (50 mg/kg BID), or nirmatrelvir+ritonavir (300+50 mg/kg BID) were administered PO, beginning 4 hours post-infection on Day 0 and continuing through Day 3. Mice were euthanized on Day 4 for determination of lung virus titers and lung histopathology. Nirmatrelvir±ritonavir prevented weight loss and reduced lung virus titers by ~1.2 $\log_{10}$ (nirmatrelvir-ritonavir) or ~1.6 $\log_{10}$ (nirmatrelvir +ritonavir) relative to vehicle-treated mice. Nirmatrelvir+ritonavir also reduced lung histopathology, while nirmatrelvir alone did not have a significant effect. Ritonavir alone did not affect weight loss, lung virus titers, or lung histopathology.

5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology properties of nirmatrelvir/ritonavir were comprehensively evaluated (Table 5). The clinical pharmacology review focused on determining dosing recommendations for specific populations including moderate renal and hepatic impairment (Section 8.1.2 and Section 8.1.3) and providing recommendations for clinical management of drug-drug interactions (Section 8.2.2).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor. Ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.
Mechanism of action	Nirmatrelvir inhibits SARS-CoV-2 M^{pro} and renders it incapable of processing polyprotein precursors, preventing viral replication. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.
Active moieties	Nirmatrelvir, ritonavir
QT prolongation	A clinical and nonclinical integrated risk assessment was submitted in lieu of a thorough QT study. In vitro *hERG* assays and an in vivo QT study in monkeys suggested that nirmatrelvir has a low risk for QT prolongation. In Phase 1 clinical Study 1001, subjects received a supratherapeutic nirmatrelvir dose of 2250 mg (divided into three doses) boosted with ritonavir 100 mg. A concentration-Qtc analysis was conducted using the PK and ECG parameters from Study 1001. The upper bounds of 90% CI for QTcF estimates across the entire concentration range were all well below 10 ms, the threshold for potential clinical and regulatory concern. A small increase in blood pressure cannot be excluded based on a numerical increase in PR which is not expected to be clinically meaningful given the short treatment duration.
General Information	
Bioanalysis	LC-MS/MS methods were validated and were used to determine the concentrations of nirmatrelvir, ritonavir and co-administered drugs in human plasma and urine. The analyses were deemed to be acceptable.
Healthy subjects versus patients	The observed plasma nirmatrelvir concentrations from EPIC-HR subjects with COVID-19 are similar to concentrations observed in the healthy subjects enrolled in study 1014 (C_{max} 3.43 µg/mL versus 2.21 µg/mL and AUC 30.40 µg*hr/mL versus 23.01 µg*hr/mL, respectively).
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. Predicted Day 5 Nirmatrelvir Exposure Parameters for Adult Subjects in EPIC-HR Following Twice-Daily Dosing With 300 mg/100 mg Nirmatrelvir/Ritonavir** **Pharmacokinetic Parameter (units)[a]** — **Nirmatrelvir[b]** C_{max} (µg/mL) — 3.43 (2.59, 4.52) AUC_{tau} (µg*hr/mL)[c] — 30.40 (22.90, 39.80) C_{min} (µg/mL) — 1.57 (1.16, 2.10) Source: Study 1005. [a.] Data presented as geometric mean (10th and 90th percentile). [b.] Based on 1,016 subjects with their post hoc PK parameters. [c.] AUC_{tau}, predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing. Abbreviations: C_{max}, predicted maximal concentration; C_{min}, predicted minimal concentration (C_{trough})

Characteristic	Drug Information
Range of effective dose(s) or exposure	Nirmatrelvir/ritonavir 300/100 mg twice daily was the only dosing regimen evaluated in the pivotal efficacy study.
Maximally tolerated dose or exposure	An MTD was not determined. The evaluated dose that achieved the highest exposure in humans was an oral dose of 2250 mg nirmatrelvir (3 doses of 750 mg each administered at 0 h, 2 h and 4 h) and 3 doses of ritonavir 100 mg administered at -12 h, 0 h, and 12 h post NIR dose.
Dose proportionality	Nirmatrelvir C_{max} and AUC increased in a less than dose proportional manner following administration of an oral suspension formulation at single ascending nirmatrelvir doses of 250 mg to 750 mg, administered with 100 mg ritonavir or multiple ascending nirmatrelvir/ritonavir doses of 75/100 mg BID to 500/100 mg BID for 10 days.
Accumulation	Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} and C_{max}, respectively, on Day 10 with 75mg to 500 mg nirmatrelvir administered twice daily with 100 mg ritonavir. Values were similar on Day 5 and Day 10.
Time to achieve steady-state	Twice daily dosing of nirmatrelvir with ritonavir over 10 days achieved steady-state on Day 2.
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed 150 mg nirmatrelvir and 100 mg ritonavir tablets were used in the pivotal efficacy study.
Absorption	
Bioavailability	The absolute bioavailability of nirmatrelvir/ritonavir is unknown.
T_{max}	Nirmatrelvir (when given with ritonavir): 3 hours[a] Ritonavir (when given with nirmatrelvir): 3.98 hours[a]
Food effect (fed/fasted) Geometric least square mean and 90% CI	Following a single oral dose of to-be-marketed oral tablet of nirmatrelvir 300 mg boosted with 3 doses of (q12h) ritonavir 100 mg administered with a high fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) meal versus fasted, the adjusted geometric means (90% CI) for nirmatrelvir AUC_{inf}, and C_{max} were 1.20 (1.09, 1.32) and 1.61 (1.39, 1.86), respectively. The median T_{max} was 2.50 hours for the fed treatment compared to 2.29 hours for the fasted treatment.
Distribution	
Volume of distribution	Nirmatrelvir (when given with ritonavir): 104.7 L[b] Ritonavir: 112.4 L[b]
Plasma protein binding	Nirmatrelvir: 69% Ritonavir: 98-99%
Drug as substrate of transporters	In vitro data indicate that nirmatrelvir is a substrate for human MDR1 (P-gp), but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.
Elimination	
Mass balance results	The excretory pathways and metabolic profile of unlabeled nirmatrelvir was evaluated in urine and feces in a mass balance trial. Nirmatrelvir concentrations were determined using quantitative LC-MS/MS bioanalysis and quantitative fluorine (^{19}F) NMR. After a single unlabeled dose of 300 mg nirmatrelvir oral suspension co-administered with 100 mg ritonavir tablet (at -12 hours, 0 hours, 12 hours, and 24 hours relative to nirmatrelvir administration), a total of 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively. The percentage of the dose excreted as total (unchanged drug) was 55.0% in urine and 27.5% in feces. After a single radiolabeled dose of 600 mg ^{14}C-ritonavir oral solution, a total of 11.3% and 86.4% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively. The percentage of the dose excreted as total (unchanged drug) was 3.5% in urine and 33.8% in feces.
Clearance (CL/F)	Nirmatrelvir (when given with ritonavir): 8.99[b] Ritonavir: 13.92[b]

Characteristic	Drug Information
Half-life	Nirmatrelvir (when given with ritonavir): 6.05[a] Ritonavir: 6.15[a]
Metabolic pathway(s)	Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir, metabolic clearance is minimal. Ritonavir undergoes major metabolism by CYP3A4 with minor contribution by CYP2D6.
Primary excretion pathways (% dose)	Nirmatrelvir (when given with ritonavir): Renal elimination Ritonavir: Fecal elimination
Intrinsic Factors and Specific Populations	
Body weight	No dosage adjustment is required based on body weight.
Age	No dosage adjustment is required based on age.
Renal impairment	A dosage adjustment of 150 mg nirmatrelvir/ 100 mg ritonavir twice daily for 5 days is recommended for patients with moderate renal impairment (eGFR 30 to <60 mL/min). No dose adjustment is required for mild renal impairment (eGFR 60 to <90 mL/min). PAXLOVID is not recommended in patients with severe renal impairment until additional data are available.
Hepatic impairment	No dosage adjustment is required in patients with mild and moderate hepatic impairment (Child-Pugh Score A and B, respectively). PAXLOVID is not recommended for use in patients with severe hepatic impairment due to a lack of pharmacokinetic or safety data in this population.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	The combination of nirmatrelvir and ritonavir is a strong inhibitor of CYP3A4. Ritonavir is a weak inhibitor of CYP2D6. Ritonavir is an inducer of CYP1A2, CYP2C8, CYP2C9 and CYP2C19.
Inhibition/induction of transporter systems	Ritonavir is an inhibitor of P-gp. Nirmatrelvir is an inhibitor of P-gp and OATP1B1.

Source: Study PF-07321332_04Nov20_113907, Study PF-07321332_09Nov20_122202, Study PF-07321332_18Oct20_102559, Study PF-07321332_18Nov20_020944, NORVIR USPI.
[a.] Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
[b.] 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice daily for 3 days.
Abbreviations: AUC, area under the curve; AUC_{inf}, area under concentration-time curve to infinity; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP, cytochrome P450; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hERG, human ether-a-go-go related gene; HIV, human immunodeficiency virus; LC-MS/MS, liquid chromatography tandem mass spectrometry; M^{pro}, main protease; MTD, maximum tolerated dose; NIR, nirmatrelvir; NMR, nuclear magnetic resonance; P-gp, P-glycoprotein; PK, pharmacokinetic; PR, pulse rate; q12h, every 12 hours; QT, interval from beginning of QRS complex to the end of the T wave; QTc, QT interval corrected for heart rate; QTcF, the corrected QT interval by Fridericia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T_{max}, time for drug to reach maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The dosing regimen for the treatment of high-risk symptomatic SARS-CoV-2 is primarily supported by the data from EPIC-HR demonstrating that the dose of nirmatrelvir/ritonavir 300/100 mg BID for 5 days is generally safe and well-tolerated and effective at reducing the risk of hospitalization/death. This dosing regimen was the only regimen evaluated in EPIC-HR and was chosen to achieve a target minimum nirmatrelvir concentration in plasma approximating the protein binding-adjusted EC_{90} value (292 ng/mL, 585 nM) for anti-SARS-CoV-2 activity in cell

culture, which was supported by antiviral activity data from a SARS-CoV-2 mouse model and simulations with a preliminary population PK model suggesting that >90% of subjects achieve a trough concentration above the nirmatrelvir EC_{90} value after the first dose. The 5-day treatment duration for immunocompetent patients was based on the interplay of viral dynamics of SARS-CoV-2 and immune response in a quantitative systems pharmacology (QSP) model. In addition, the model suggested that a longer treatment duration beyond 5 days may be beneficial for immunocompromised patients. Specifically, a treatment duration of 10 days is supported by the QSP modeling for further clinical trial evaluation (See Sections 6.3.5 and 14).

The exposure (C_{min})-response (E-R) analyses were conducted and verified by the review team using viral load (VL) data from SARS-CoV-2 positive patients who received 300/100 mg BID for 5 days in EPIC-HR. VL over time in study subjects was evaluated using viral RNA levels measured via real-time, reverse transcription-polymerase chain reaction (RT-PCR). Change from baseline (CFB) in VL at Day 5 was used to assess the E-R relationship. No E-R relationship was observed for Day 5 CFB VL and nirmatrelvir concentrations which could be attributed to greater than 95% of subjects having nirmatrelvir concentrations ≥3-5 times the EC_{90} value, with a very limited number of lower concentrations (see Section 14, Table 7, and Figure 1). Few immunocompromised patients were included in the E-R analyses which limited the ability to inform the potential effect of immune function on E-R.

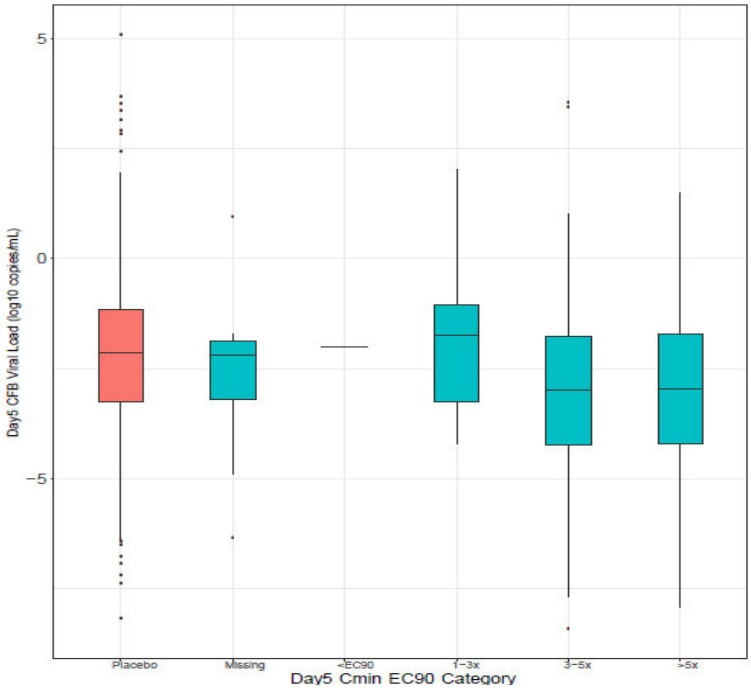
A scatterplot with the associated linear regression line of the VL response versus nirmatrelvir concentrations including all EPIC-HR subjects in the E-R analysis population is shown in Figure 2. In a small subset of subjects from the active treatment group who were hospitalized (n=6, represented by red dots), nirmatrelvir concentrations were within the range of those in non-hospitalized patients and were all below the median predicted Day 5 nirmatrelvir C_{min} and below 5 times the EC_{90} value. However, this trend should be interpreted with caution due to the very low sample size of hospitalized subjects and the high degree of variability in the VL data.

Table 7. Summary of Day 5 Change From Baseline by Day 5 C_{min} of Nirmatrelvir Relative to EC_{90} Multiples

EC_{90}	N	Day 5 CFB in VL- Median (log_{10}copies/mL)
Placebo group	740	-2.13
Missing exposure	8	-2.18
<EC_{90}	1	-2.00
1-3x EC_{90}	31	-1.73
3-5x EC_{90}	332	-3.00
>5x EC_{90}	362	-2.97

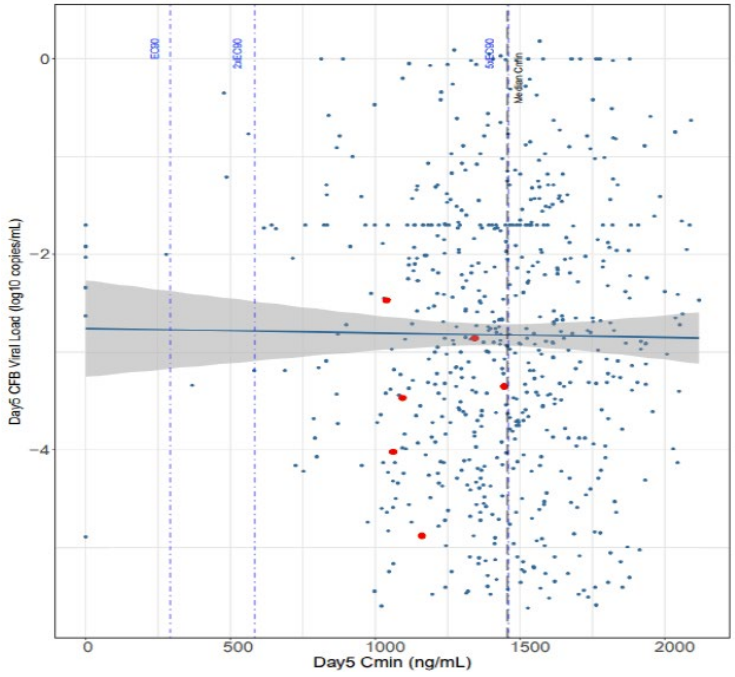
Source: EPIC-HR.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; EC_{90} 90% maximal effective concentration; log, logarithm; N, total number of subjects; VL, viral load

Figure 1. Relationship Between Day 5 Change From Baseline in Viral Load and Day 5 C_{min} of Nirmatrelvir Relative to EC_{90} Value



Source: EPIC-HR.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; EC_{90}, 90% maximal effective concentration; log, logarithm

Figure 2. Day 5 Change From Baseline Versus Day 5 C_{min} (Hospitalizations Displayed)



Source: EPIC-HR.
Note: Subjects from active treatment group who were hospitalized are represented by red dots. Linear regression line shown in solid blue with associated 95% confidence interval in gray. Median predicted Day 5 C_{min} shown with black dashed line; EC_{90} reference lines shown with blue dot-dash lines.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; EC_{90}, 90% maximal effective concentration; log, logarithm

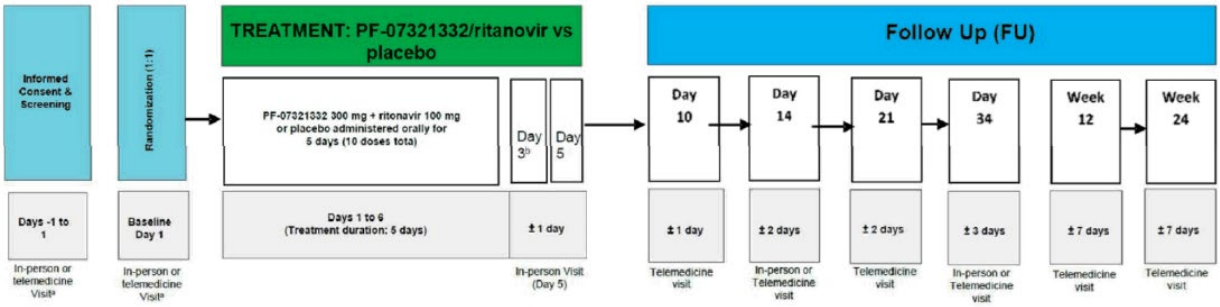
6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. EPIC-HR C4671005

6.2.1.1. Design, EPIC-HR

EPIC-HR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19, who were unvaccinated against COVID-19 and at high risk for progression to severe disease (see Section 6.2.1.2 for protocol-defined risk factors for progression to severe disease). Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID or placebo orally q12h for 5 days. Randomization was stratified by geographic region and whether subjects had received or were expected to receive COVID-19 therapeutic mAb treatment (yes/no) at the time of randomization. The total study duration was up to 24 weeks. The study schematic is summarized in Figure 3.

Figure 3. Study Design of EPIC-HR



Source: EPIC-HR Clinical Study Report, Figure 1.2.
[a.] The baseline and screening visits may be a combination of in-person and telemedicine visits.
[b.] The Day 3 visit must be conducted in-person for the first 60 subjects (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.
Abbreviations: ECG, electrocardiogram; FU, follow up; HCP, healthcare provider; PK, pharmacokinetic

The primary analysis population was updated in protocol amendment 2 (August 2, 2021) to include only those with onset of COVID-19 symptoms ≤3 days and the total sample size was increased from 2260 to approximately 3000. Sites in India were terminated (on September 22, 2021) due to a blinded data review of a >90% rate of serology positive subjects at baseline. Site 1470 was terminated for GCP noncompliance.

Enrollment of subjects who had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25%. Enrollment of subjects who had COVID-19 symptom onset >3 days prior to randomization was expected to be approximately 25% and was to be limited to approximately 1000.

An independent external data monitoring committee (E-DMC) reviewed unblinded safety data on an ongoing basis throughout the trial duration, and for a sentinel cohort of the first 60 subjects after completion through Day 10. In addition, the E-DMC conducted a proof-of-concept assessment using viral RNA shedding data from approximately 200 subjects from the modified

intent-to-treat (mITT) analysis population through Day 5, and a formal interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 45% of subjects in the mITT analysis population completed the Day 28 assessments. The E-DMC determined that the prespecified criteria for stopping the trial due to overwhelming efficacy had been achieved at the 45% interim efficacy analysis (data cutoff October 26, 2021) and further enrollment in the trial was subsequently stopped on November 5, 2021. The pre-planned second interim analysis at 70% enrollment was cancelled. The final efficacy analysis was conducted as a supportive analysis after all subjects completed the Day 34 visit. The follow-up analysis was performed after all subjects completed the Week 24 visit.

During the NDA review, data anomalies were observed from Site 1274. Data from this site were removed from the review. In addition, data from Site 1470 were also removed from the review due to GCP noncompliance as noted above. Detailed discussion on data anomalies can be found in Section 6.3.1.

6.2.1.2. Eligibility Criteria, EPIC-HR

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.1.

Inclusion Criteria

1. ≥18 years of age.
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Specified signs/symptoms include: cough, shortness of breath or difficulty breathing, fever or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.
4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
   - ≥60 years of age
   - Body mass index (BMI) >25 kg/m2
   - Current smoker and history of at least 100 lifetime cigarettes
   - Immunosuppressive disease OR prolonged use of immune-weakening medications
   - Chronic lung disease
   - Known diagnosis of hypertension
   - Cardiovascular disease
   - Type 1 or Type 2 diabetes mellitus
   - Chronic kidney disease (CKD)
   - Sickle cell disease
   - Neurodevelopmental disorders
   - Active cancer
   - Medical-related technological dependence

Exclusion Criteria

1. History of hospitalization for the medical treatment of COVID-19.
2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization.
3. Prior to current disease episode, any confirmed SARS-CoV-2 infection.
4. Known medical history of active liver disease.
5. Receiving dialysis or have known moderate to severe renal impairment (i.e., eGFR <45 mL/min).
6. Known HIV infection with viral load > 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).
7. Received or expected to receive convalescent COVID-19 plasma.
8. Received or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.
9. Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study intervention used in this study.
10. Current or expected use of any medications or substances highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last PAXLOVID dose.
11. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment.
12. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - Aspartate aminotransaminase (AST) or alanine aminotransferase (ALT) level ≥2.5 X upper limit of normal (ULN)
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome)
    - eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm^3
13. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.
14. Females who are pregnant or breastfeeding.

6.2.1.3. Statistical Analysis Plan, EPIC-HR

The following analysis populations were included:

- **Full Analysis Set (FAS):** All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered.
- **Modified Intent-To-Treat (mITT):** All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

- **Modified Intent-To-Treat 1 (mITT1):** All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were dosed to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 symptom onset.
- **Modified Intent-To-Treat 2 (mITT2):** All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset. Subjects were analyzed according to the study intervention to which they were randomized.
- **Per-Protocol (PP):** All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.
- **Safety Analysis Set (SAF):** All subjects who receive at least 1 dose of study intervention. Subjects were analyzed according to the study intervention they received.

The pre-specified primary efficacy analysis population was the mITT population.

The primary efficacy endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population. The first key secondary efficacy endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population. The second key secondary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 in the mITT population. Following the positive test of the primary endpoint, the first key secondary endpoint, and the second key secondary endpoint, the following secondary endpoints were subsequently tested in the mITT population following the Hochberg procedure:

1. Time to sustained resolution of all targeted signs/symptoms through Day 28.
2. Proportion of subjects with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.
3. Number of COVID-19 related medical visits.

The following additional secondary endpoints were also evaluated:

1. Proportion of subjects with severe signs/symptoms attributed to COVID-19 through Day 28.
2. Duration of each targeted COVID-19 sign/symptom.
3. Progression to a worsening status in 1 or more self-reported COVID-19 associated symptoms through Day 28.
4. Proportion of subjects with death (all cause) through Week 24.
5. Viral titers measured via RT-PCR in nasal swabs over time.
6. Number of days in hospital and intensive care unit (ICU) stay in subjects with COVID-19 related hospitalization.

6.2.1.4. Results of Analyses, EPIC-HR

After excluding Sites 1274 and 1470, 2256 subjects were screened and 2113 were randomized. Conclusion of efficacy was based on interim analysis as pre-specified in the protocol. Results of the complete EPIC-HR trial are summarized in this section. All p-values displayed in this section are nominal p-values. Refer to Section 16.2.1 for interim analyses results.

Table 8. Subject Disposition, EPIC-HR

Disposition Outcome	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Subjects randomized	1049 (100.0)	1064 (100.0)
FAS population	1049 (100.0)	1064 (100.0)
mITT population	671 (64.0)	647 (60.8)
mITT1 population	977 (93.1)	989 (93.0)
mITT2 population	1038 (99.0)	1053 (99.0)
PP population	646 (61.6)	616 (57.9)
Safety population	1038 (99.0)	1053 (99.0)
Discontinued study drug[a]	63 (6.0)	85 (8.0)
Adverse event (AE)	21 (2.0)	45 (4.2)
Withdrawal by subject	30 (2.9)	27 (2.5)
No longer meets eligibility criteria	3 (0.3)	1 (0.1)
Medication error without associated adverse event	0	1 (0.1)
Other	9 (0.9)	11 (1.0)
Discontinued study[a]	73 (7.0)	85 (8.0)
Withdrawal by subject	41 (3.9)	44 (4.1)
Lost to follow-up	20 (1.9)	16 (1.5)
Death	0	15 (1.4)
Other	12 (1.1)	10 (0.9)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
[a.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline demographic and clinical characteristics are listed in Table 9. The two groups had similar distributions in these characteristics. All subjects were between 18 and 88 years of age. Approximately 49% of patients were female and 38% of subjects were from the United States.

Table 9. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-HR

Characteristic	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Sex		
Female	523 (49.9)	521 (49.0)
Male	526 (50.1)	543 (51.0)
Age, years		
Mean (SD)	44.8 (15.3)	45.9 (15.6)
Median (min, max)	44.0 (18.0, 86.0)	46.0 (18.0, 88.0)
Age group, years		
18 to 44	540 (51.5)	505 (47.5)
45 to 59	310 (29.6)	320 (30.1)
60 to 64	70 (6.7)	105 (9.9)
65 to 74	96 (9.2)	103 (9.7)
≥75	33 (3.1)	31 (2.9)
Race		
American Indian or Alaska Native	96 (9.2)	95 (8.9)
Asian	154 (14.7)	160 (15.0)
Black or African American	53 (5.1)	36 (3.4)
Multiple	1 (0.1)	2 (0.2)
White	736 (70.2)	760 (71.4)
Unknown or Missing	9 (0.9)	11 (1.0)

Characteristic	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Ethnicity		
Hispanic or Latino	429 (40.9)	443 (41.6)
Not Hispanic or Latino	615 (58.6)	614 (57.7)
Not Reported	5 (0.5)	7 (0.7)
Region		
United States	392 (37.4)	403 (37.9)
Europe	334 (31.8)	335 (31.5)
India	95 (9.1)	98 (9.2)
Rest of the World	228 (21.7)	228 (21.4)
BMI, kg/m^2		
Mean (SD)	29.0 (5.4)	29.2 (5.7)
Median (min, max)	28.1 (16.6, 58.1)	28.3 (16.0, 59.1)
Missing, n (%)	0	1 (0.1)
BMI group, kg/m^2		
<25	210 (20.0)	210 (19.7)
25 to <30	471 (44.9)	466 (43.8)
30 to <35	250 (23.8)	250 (23.5)
35 to <40	71 (6.8)	79 (7.4)
≥40	47 (4.5)	58 (5.5)
Missing	0	1 (0.1)
Duration since first symptom, days		
≤3	722 (68.8)	696 (65.4)
>3	327 (31.2)	368 (34.6)
COVID-19 mAb treatment		
Received / expected to receive	61 (5.8)	65 (6.1)
Not received / not expected to receive	988 (94.2)	999 (93.9)
Baseline serology status		
Negative	505 (48.1)	529 (49.7)
Positive	523 (49.9)	514 (48.3)
Unknown	21 (2.0)	21 (2.0)
Baseline Viral RNA (NP samples, log_{10} copies/mL)		
Mean (SD)	4.76 (2.89)	4.67 (2.88)
Median (min, max)	5.52 (0, 9.16)	5.39 (0, 9.15)
Missing, n (%)	36 (3.4)	37 (3.5)

Source: Reviewer's Analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mAb, monoclonal ant bodies; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; NP, nasopharyngeal; RNA, ribonucleic acid; SD, standard deviation

Primary Efficacy Endpoint

Table 10 displays analysis results for COVID-19 related hospitalization or death from any cause through Day 28, in the mITT (primary endpoint), mITT1 (first key secondary endpoint), and mITT2 populations. After accounting for premature study discontinuation by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID demonstrated a 5.6% (95% CI: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72%, 93%) relative reduction compared to placebo, in mITT1 population. All three analyses had p-values <0.0001. The trial was terminated early for efficacy as planned. Interim analyses results for efficacy can be found in Section 16.2.1.

Table 10. Proportion of Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-HR

mITT[a]	**PAXLOVID**	**Placebo**
Analysis	**N=671**	**N=647**
Subjects with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[d]	-6.1 (-8.2, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b]	**PAXLOVID**	**Placebo**
Analysis	**N=977**	**N=989**
Subjects with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.3, -4.0)	
Two-sided nominal p-value	<0.0001	
mITT2[c]	**PAXLOVID**	**Placebo**
Analysis	**N=1038**	**N=1053**
Subjects with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.0, -3.8)	
Two-sided nominal p-value	<0.0001	

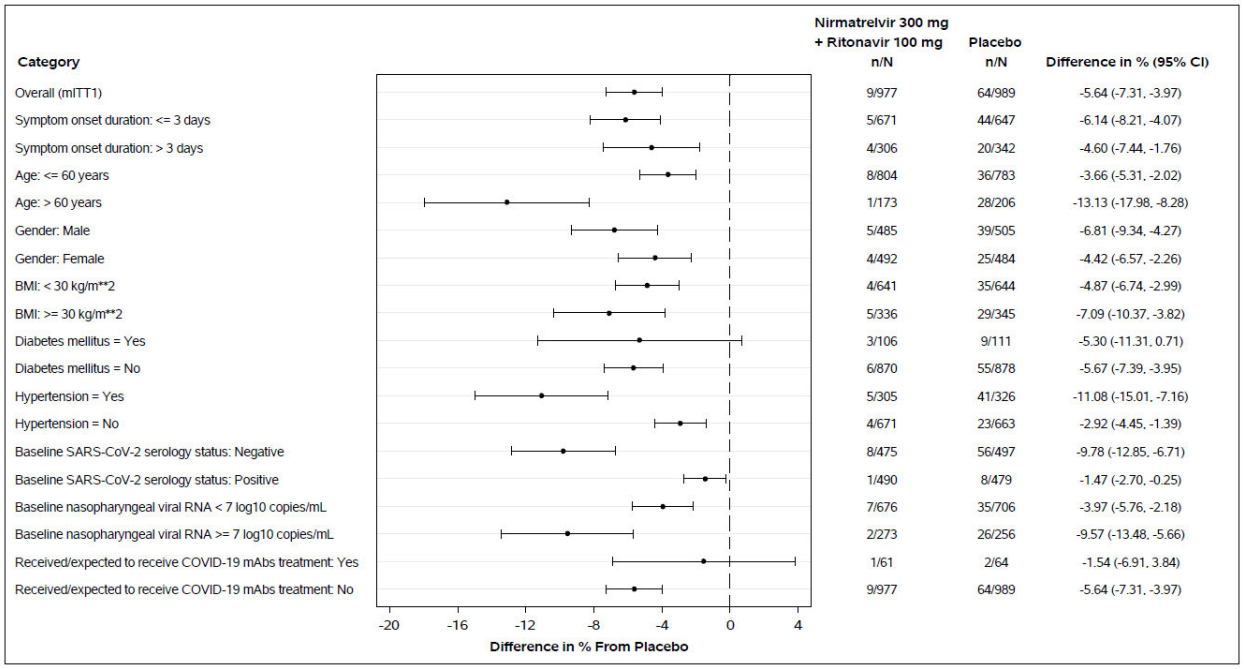
Source: Reviewer's analysis on ADTTE dataset, excluding subjects from site 1274 and site 1470
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset
[d.] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

The below sensitivity analyses were conducted for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT, mITT1, and mITT2 populations; results were consistent with the above findings in Table 10. Detailed findings of these sensitivity analyses are available in Section 16.2.2.

- For subjects who enrolled more than once in EPIC-HR or enrolled in EPIC-HR and in one or two other Phase 2/3 PAXLOVID trials, data from a duplicate subject's first enrollment within this trial were included and data from a duplicate subject's subsequent enrollments were excluded.
- Sites in India were excluded.
- Subjects who were lost to follow up before Day 21 were hypothetically assumed to have experienced both COVID-19 related hospitalization or death in a worst-case scenario.
- Subjects who did not complete Day 28 follow up and discontinued study treatment due to AE were hypothetically assumed to have experienced both COVID-19 related hospitalization and death in a worst-case scenario.

As shown in Figure 4, similar trends have been observed across subgroups of subjects. Additional subgroup analyses are available in Section 16.2.3.

Figure 4. Subgroup Analysis of Adults With COVID-19 Dosed Within 5 Days of Symptom Onset With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-HR



Source: Figure 84a.67a.3, NDA 217188 SDN 75.
Note: All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in the category of analysis set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Refer to review issue Section 6.3.1 on discussion of data anomalies; additional sensitivity analyses are available in Section 16.1.

Symptom Diary-Related Efficacy Endpoints

Subjects were provided an electronic handheld device or used their own device to record daily COVID-19 signs and symptoms in the study diary through Day 28. While this subsection summarizes symptom diary related efficacy endpoint data, these results should be interpreted with caution based on the following limitations:

- Approximately 19% subjects in the mITT2 population missed more than 25% symptom diary entries (18% in PAXLOVID group and 19% in placebo group).
- On average, there were 18% missing symptom diary entries in the overall mITT2 population (see Section 16.4.1 for details).
- Approximately 41% subjects in the mITT2 population were enrolled at sites with symptom data collection issues with respect to PIN codes (after excluding site 1274 and site 1470, see Section 16.1 for details).

The reasons for missing symptom diary data are complicated. Some subjects stopped completing symptom diary after having absence of symptoms, while some subjects did not properly complete the diary when having severe disease progression (e.g., being hospitalized).

Targeted COVID-19 symptoms for analysis included cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.

Table 11 displays analysis results for the endpoint of time to sustained symptom alleviation, in the mITT (second key secondary endpoint), mITT1 and mITT2 populations. Sustained alleviation was defined as the first of four consecutive days when all symptoms scored as moderate or severe at study entry were scored as mild or absent and all symptoms scored mild or absent at study entry were scored as absent. The first day of the four consecutive-day period will be considered the first event date. Definition of this endpoint was related to baseline symptom severity, making it more difficult to interpret the findings compared to the time to sustained resolution endpoint discussed later in the review.

The PAXLOVID group demonstrated superiority to the placebo group in all three analyses. This result is influenced by the fact that the PAXLOVID group had fewer hospitalization and death events, and those events were considered failures in the sustained symptom alleviation endpoint and censored on Day 25.

Table 11. Time to Sustained Symptom Alleviation Through Day 28, EPIC-HR

Sustained Symptom Alleviation in mITT[a]	**PAXLOVID N=666**	**Placebo N=645**
Subjects with sustained symptom alleviation, n (%)	507 (76.1)	436 (67.6)
Median time to sustained symptom alleviation by Day 28 (95% CI)	12 (12, 13)	15 (13, 16)
Two-sided nominal p-value	<0.0001	
Sustained Symptom Alleviation in mITT1[b]	**PAXLOVID N=970**	**Placebo N=986**
Subjects with sustained symptom alleviation, n (%)	705 (72.7)	640 (64.9)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (12, 13)	15 (14, 16)
Two-sided nominal p-value	<0.0001	
Sustained Symptom Alleviation in mITT2[c]	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with sustained symptom alleviation, n (%)	743 (72.1)	680 (64.8)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (12, 13)	16 (15, 17)
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from log rank test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 12 displays analysis results for the endpoint of time to sustained symptom resolution, in the mITT (secondary endpoint), mITT1 and mITT2 populations. Sustained resolution was

defined as the time when all targeted symptoms were scored as absent for four consecutive days. The first day of the four consecutive-day period was considered the first event date.

The PAXLOVID group was superior to the placebo group in all three analyses. This result is influenced by the fact that the PAXLOVID group had fewer hospitalization and death events, while those events were considered failures in the sustained symptom resolution endpoint and censored on Day 25.

Table 12. Time to Sustained Symptom Resolution Through Day 28, EPIC-HR

Sustained Symptom Resolution in mITT[a]	PAXLOVID N=666	Placebo N=645
Subjects with sustained symptom resolution, n (%)	445 (66.8)	388 (60.2)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (14, 17)	18 (17, 20)
Two-sided nominal p-value	0.0026	
Sustained Symptom Resolution in mITT1[b]	**PAXLOVID N=970**	**Placebo N=986**
Subjects with sustained symptom resolution, n (%)	619 (63.8)	566 (57.4)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (15, 18)	19 (18, 20)
Two-sided nominal p-value	0.0004	
Sustained Symptom Resolution in mITT2[c]	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with sustained symptom resolution, n (%)	654 (63.4)	603 (57.4)
Median time to sustained symptom resolution by Day 28 (95% CI)	17 (15, 18)	19 (18, 20)
Two-sided nominal p-value	0.0004	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from log rank test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

In the mITT2 population, approximately 15% of subjects from both arms who reached sustained symptom resolution reported at least one day of having any mild or worse symptom, after reaching sustained resolution. However, it is not clear if those symptoms were relapse of previously resolved symptoms or symptoms from new/other infection. Refer to the review issue section COVID-19 rebound discussion for more analyses on symptom rebound (Section 6.3.6).

It was noted that three placebo subjects reported absence of all targeted symptoms for 4-7 consecutive days (not missing data) immediately preceding COVID-19 related hospitalization. Although these subjects were considered not recovered in the above analyses, this finding suggests that the symptom diary data may not be as robust/interpretable as the COVID-19 related hospitalization/death data.

Time to sustained alleviation and time to sustained resolution for each targeted symptom were evaluated. Details can be found in Section 16.2.4.

Table 13 summarizes analysis results for the endpoint of proportion of any severe targeted signs and symptoms attributed to COVID-19 through Day 28 in the mITT (secondary endpoint), mITT1 and mITT2 populations. The two treatment groups had similar percentages, with

percentages in the PAXLOVID group being numerically lower. Note that this analysis did not make adjustment on difference in symptom severity at baseline or take into account hospitalization or death events, which limits the interpretability of the results. Only 36 hospitalized subjects in the mITT2 population (out of 76 hospitalized subjects in total) reported any severe targeted symptoms through Day 28.

Table 13. Proportion of Subjects With Any Severe Targeted Signs and Symptoms Attributed to COVID-19 Through Day 28, EPIC-HR

mITT[a] Analysis	PAXLOVID N=666	Placebo N=645
Subjects with event, n (%)	121 (18.2)	134 (20.8)
Two-sided nominal p-value	0.2332	
mITT1[b] Analysis	**PAXLOVID N=970**	**Placebo N=986**
Subjects with event, n (%)	191 (19.7)	210 (21.3)
Two-sided nominal p-value	0.3786	
mITT2[c] Analysis	**PAXLOVID N=1031**	**Placebo N=1050**
Subjects with event, n (%)	213 (20.7)	229 (21.8)
Two-sided nominal p-value	0.5213	

Source: Reviewer's analysis on ADSO dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from Pearson's Chi-squared test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 14 summarizes analysis results for the endpoint of proportion of subjects with progression to a worsening status in one or more self-reported COVID-19-associated targeted symptoms through Day 28 in the mITT (secondary endpoint), mITT1 and mITT2 populations. The two treatment groups had similar percentages, with percentages in the PAXLOVID group being numerically higher. Note that this analysis did not take hospitalization or death events into account, which limits the interpretability of the results.

Table 14. Proportion of Subjects With Progression to Worsening Status in 1 or More Self-Reported COVID-19 Associated Targeted Symptoms Through Day 28, EPIC-HR

mITT[a] Analysis	PAXLOVID N=666	Placebo N=645
Subjects with event, n (%)	507 (76.1)	483 (74.9)
Two-sided nominal p-value	0.6010	
mITT1[b] Analysis	**PAXLOVID N=970**	**Placebo N=986**
Subjects with event, n (%)	735 (75.8)	737 (74.7)
Two-sided nominal p-value	0.5988	

mITT2[c] Analysis	PAXLOVID N=1031	Placebo N=1050
Subjects with event, n (%)	787 (76.3)	790 (75.2)
Two-sided nominal p-value	0.5597	

Source: Reviewer's analysis on ADSO dataset, excluding subjects from site 1274 and site 1470.
Note: P-values calculated from Pearson's Chi-squared test.
Note: Subjects with no symptom diary data were not included in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Secondary Efficacy Endpoint: Proportion of Subjects With a Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5

Table 15 summarizes analysis results for the endpoint of proportion of subjects with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 in the mITT (secondary endpoint), mITT1 and mITT2 populations. Subjects who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline, but the difference between two treatment groups was not statistically significant, with the PAXLOVID group having a numerically higher odds ratio.

Table 15. Subjects With Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5, EPIC-HR

mITT[a] Oxygen Saturation	PAXLOVID N=671	Placebo N=647
Subjects with Day 1 <95%, n	44	52
<95% at Day 5	11	13
≥95% at Day 5	30	35
Missing at Day 5	3	4
Subjects with Day 1 ≥ 95%, n	627	595
<95% at Day 5	11	22
≥95% at Day 5	582	530
Missing at Day 5	34	43
Odds ratio for Day 5 vs Day 1 (95% CI)	19.4 (7.8, 48.3)	8.9 (4.2, 19.3)
Two-sided nominal p-value	0.1997	
mITT1[b] Oxygen Saturation	**PAXLOVID N=977**	**Placebo N=989**
Subjects with Day 1 <95%, n	65	77
<95% at Day 5	18	24
≥95% at Day 5	40	44
Missing at Day 5	7	9
Subjects with Day 1 ≥95%, n	912	912
<95% at Day 5	18	35
≥95% at Day 5	835	799
Missing at Day 5	59	78
Odds ratio for Day 5 vs Day 1 (95% CI)	20.9 (10.1, 43.2)	12.5 (6.8, 22.7)
Two-sided nominal p-value	0.2810	

mITT2[c] Oxygen Saturation	PAXLOVID N=1038	Placebo N=1053
Subjects with Day 1 < 95%, n	69	87
<95% at Day 5	19	27
≥95% at Day 5	42	50
Missing at Day 5	8	10
Subjects with Day 1 ≥95%, n	969	966
<95% at Day 5	19	38
≥95% at Day 5	887	847
Missing at Day 5	63	81
Odds ratio for Day 5 vs Day 1 (95% CI)	21.1 (10.4, 42.8)	12.0 (6.8, 21.3)
Two-sided nominal p-value	0.2226	

Source: Reviewer's analysis on ADVS dataset, excluding subjects from site 1274 and site 1470.
Note: p-values calculated from Breslow-Day test. Subjects with missing Day 5 data were excluded in the analyses.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Secondary Efficacy Endpoint: COVID-19 Related Medical Visits Through Day 28

Table 16 summarizes analysis results for COVID-19 related medical visits in the mITT (secondary endpoint), mITT1 and mITT2 populations. Analyses were conducted to compare the event rates between treatment groups, rather than total number of visits. Comparisons between arms using the total number of medical visits may not be clinically meaningful, given that a hospital visit for more than one day is considered as one visit in this dataset. The PAXLOVID group was superior to the placebo group in all three analyses.

Table 16. Proportion of Subjects With COVID-19 Related Medical Visits, EPIC-HR

Medical Visits in mITT[a]	PAXLOVID N=671	Placebo N=647
Subjects with event, n (%)	10 (1.5)	52 (8.0)
Total number of medical visits across all subjects	22	81
Two-sided nominal p-value	<0.0001	
Medical Visits in mITT1[b]	**PAXLOVID N=977**	**Placebo N=989**
Subjects with event, n (%)	22 (2.3)	83 (8.4)
Total number of medical visits across all subjects	40	128
Two-sided nominal p-value	<0.0001	

Medical Visits in mITT2[c]	PAXLOVID N=1038	Placebo N=1053
Subjects with event, n (%)	25 (2.4)	91 (8.6)
Total number of medical visits across all subjects	45	144
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADHOSP dataset, excluding subjects from site 1274 and site 1470.
Note: Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19 Related-Hospitalization (ICU and non-ICU stays). The medical visits and hospitalization events are limited through Day 34 visit.
Note: p-values calculated from Pearson's Chi-squared test with continuity correction.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Other Endpoints

Refer to Section 6.3.2 and Section 6.3.3 for detailed analyses on viral RNA level related endpoints.

Table 17 displays analyses results for death from any cause through Week 24 in the mITT (secondary endpoint), mITT1 and mITT2 populations. No deaths were reported in the PAXLOVID group. The PAXLOVID group was superior to the placebo group in all three analyses.

Table 17. Proportion of Subjects With Death From Any Cause Through Week 24, EPIC-HR

Death in mITT[a]	PAXLOVID N=671	Placebo N=647
Subjects with event, n (%)	0	11 (1.7)
Two-sided nominal p-value	0.0004	
Death in mITT1[b]	**PAXLOVID N=977**	**Placebo N=989**
Subjects with event, n (%)	0	15 (1.5)
Two-sided nominal p-value	<0.0001	
Death in mITT2[c]	**PAXLOVID N=1038**	**Placebo N=1053**
Subjects with event, n (%)	0	15 (1.4)
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1274 and site 1470.
Note: p-values calculated from Fisher's exact test.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 18 summarizes analysis results for the duration of hospital and ICU stays in subjects with COVID-19 related hospitalization in the mITT (secondary endpoint), mITT1 and mITT2 populations. No subject in the PAXLOVID group reported any ICU visits.

Table 18. Duration of COVID-19 Related Hospitalization, EPIC-HR

mITT[a] Outcomes	PAXLOVID N=671	Placebo N=647
Duration of hospitalization visits (Days)		
Subjects with event, n	4	55
Mean (SD)	11.8 (3.4)	12.4 (12.7)
Median (range)	13 (7, 16)	9 (3, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	8
Mean (SD)		14.5 (17.0)
Median (range)		10 (3, 55)
mITT1[b] Outcomes	**PAXLOVID N=977**	**Placebo N=989**
Duration of hospitalization visits (Days)		
Subjects with event, n	9	63
Mean (SD)	9.4 (3.8)	12.0 (11.2)
Median (range)	8 (5, 16)	9 (2, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	9
Mean (SD)		14.1 (16.0)
Median (range)		10 (3, 55)
mITT2[c] Outcomes	**PAXLOVID N=1038**	**Placebo N=1053**
Duration of hospitalization visits (Days)		
Subjects with event, n	10	65
Mean (SD)	9.5 (3.6)	11.8 (11.0)
Median (range)	9 (5, 16)	9 (2, 63)
Duration of ICU visits (Days)		
Subjects with event, n	0	9
Mean (SD)		14.1 (16.0)
Median (range)		10 (3, 55)

Source: Reviewer's analysis on ADHOSP dataset, excluding subjects from site 1274 and site 1470.
Note: Hospitalization visits are not limited through Day 28.
[a.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibody; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

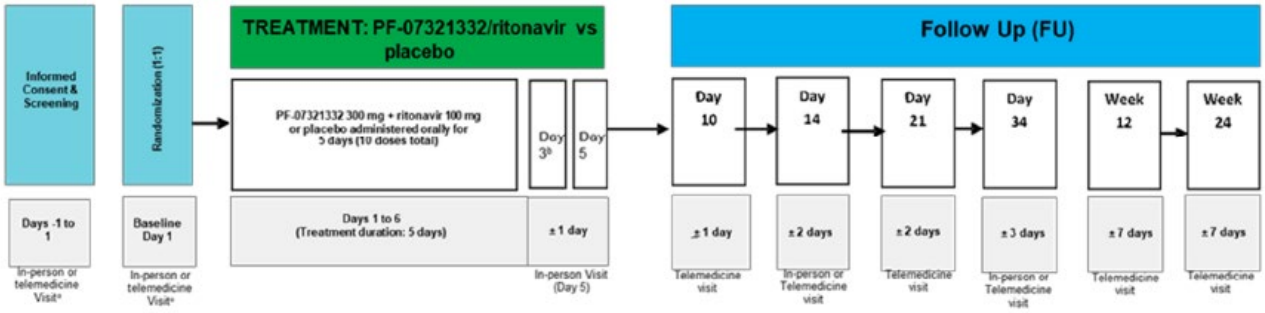
6.2.2. EPIC-SR C4671002

6.2.2.1. Design, EPIC-SR

EPIC-SR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19. The trial enrolled COVID-19-vaccinated subjects who were at high risk for progression to severe disease and unvaccinated subjects who had no risk factors for progression to severe disease. Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID (nirmatrelvir 300mg co-administered with ritonavir 100mg) or placebo orally q12h for 5 days. Randomization was stratified by geographic region, vaccination status,

and COVID-19 symptom onset (≤3 days versus >3 days). The total study duration was up to 24 weeks. The study schematic is summarized in Figure 5.

Figure 5. Study Design of EPIC-SR



Source: EPIC-SR Interim Clinical Study Report, Figure 1.
[a.] The baseline and screening visits may be a combination of in-person and telemedicine visits.
[b.] The Day 3 visit will only be conducted in-person only if a PK sample (not using Tasso) is collected by an HCP or at the discretion of the investigator.
Abbreviations: FU, follow up; HCP, healthcare provider; PK, pharmacokinetic

The primary analysis population was updated in protocol amendment 3 (August 3, 2021) to include only those with onset of COVID-19 symptoms ≤3 days and the sample size was increased from 800 to 1140. The testing hierarchy of secondary efficacy endpoints was updated in protocol amendment 4 (November 23, 2021), adding COVID-19 related hospitalization or death from any cause through Day 28 in all treated subjects as a key secondary endpoint.

An independent E-DMC reviewed unblinded safety data on an ongoing basis throughout the duration of the trial, and for a sentinel cohort of the first 100 subjects after completion through Day 10. In addition, the E-DMC conducted a proof-of-concept assessment using viral RNA shedding data from approximately 200 subjects in the mITT analysis population through Day 5, and an interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 45% of subjects in the mITT analysis population completed the Day 28 assessments. The originally planned enrollment was completed on November 9, 2021. The third interim analysis utilizing the December 19, 2021, dataset [100% planned enrollment through protocol amendment 4, EPIC-SR (2021/pre-Omicron)] was submitted to support this NDA (results summarized in Section 6.2).

Based on the outcome from this trial's interim analysis and the final results of EPIC-HR, this trial was modified to re-open enrollment in 2022 to collect information on the clinical endpoint of hospitalization or death at a time that the Omicron variant was the dominating circulating variant, with a plan to increase total sample size to 1980 under amendment 5. Enrollment in 2022 was started in March and terminated in June due to no hospitalization or death events reported after reopening. Additional datasets providing information on the 287 subjects enrolled in 2022 [EPIC-SR (2022/Omicron)] were submitted during the NDA review process to support analyses related to review issues described in Section 6.3.

During the NDA review, data anomalies were observed in Site 1281. Data from this site are removed from the review. In addition, data from Site 1488 are removed from the review due to GCP noncompliance. Detailed discussion on data anomalies can be found in Section 6.3.1. In the

EPIC-SR 2022/Omicron datasets, data anomalies were observed in Site 1157 and Site 1197 leading to their removal from specific Omicron-related analyses.

6.2.2.2. Eligibility Criteria, EPIC-SR

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.2.

Inclusion Criteria

1. ≥18 years of age.
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization, and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Specified signs/symptoms include: cough, shortness of breath or difficulty breathing, fever or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose.

Exclusion Criteria

1. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:

Note: Subjects with these conditions who were fully vaccinated (as defined by local regulations and practices) were considered to be at lower risk of developing severe disease and were therefore considered eligible before Amendment 5.

- ≥60 years of age
- BMI >25
- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
- Chronic lung disease (if asthma, requires daily prescribed therapy)
- Known diagnosis of hypertension
- Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass
- Type 1 or Type 2 diabetes mellitus
- CKD
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
- Medical-related technological dependence (e.g., CPAP [not related to COVID-19])

2. Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications
3. History of hospitalization for the medical treatment of COVID-19
4. Current need for hospitalization or anticipated need for hospitalization within 48 hour after randomization
5. Prior to current disease episode, any confirmed SARS-CoV-2 infection
6. Known medical history of active liver disease
7. Receiving dialysis or have known renal impairment
8. Known HIV infection with viral load >400 copies/mL or taking prohibited medications for HIV treatment
9. Received or expected to receive mAb treatment or convalescent COVID-19 plasma
10. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PAXLOVID
11. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment
12. Received or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit, except for subjects with any of the underlying medical conditions specified in Exclusion criterion #1 who are fully vaccinated prior to study entry

Note: Fully vaccinated subjects with underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 must not receive a SARS-CoV-2 vaccine booster between screening and the Day 34 visit.

13. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN
    - Total bilirubin ≥2X ULN (≥3X ULN for Gilbert's syndrome)
    - eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3
14. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.
15. Females who are pregnant or breastfeeding.

6.2.2.3. Statistical Analysis Plan, EPIC-SR

The following analysis populations were included:

- **FAS**: All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered.

- **mITT**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and were dosed within ≤3 days of COVID-19 symptom onset.
- **mITT1**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention. Subjects were analyzed according to the study intervention to which they were randomized.
- **PP**: All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.
- **SAF**: All randomized subjects who received at least one dose of study intervention. Subjects were analyzed according to the study intervention they received.

The pre-specified primary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 (see Section 6.2.1.4 for the full definition), evaluated in the mITT population: this primary endpoint was not met. Results of the following secondary efficacy endpoints in the mITT1 population were submitted to support the NDA:

- Time to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28
- Time to sustained resolution of all targeted COVID-19 signs/symptoms through Day 28
- Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28
- Proportion of subjects with severe signs/symptoms attributed to COVID-19 through Day 28
- Progression to a worsening status in one or more self-reported COVID-19 associated symptoms through Day 28
- Number of COVID-19 related medical visits through Day 28
- Number of days in hospital and ICU stay in subjects with COVID-19 related hospitalization through Day 28
- Proportion of subjects with death (all cause) through Week 24
- Viral titers measured via RT-PCR in nasal swabs over time

6.2.2.4. Results of Analyses, EPIC-SR

After excluding Site 1281 and Site 1488, 1165 subjects were screened and 1075 were randomized in 2021. Results of EPIC-SR (2021/pre-Omicron) analyses are summarized in this section.

Table 19. Subject Disposition, EPIC-SR

Disposition Outcome	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Subjects randomized	544 (100.0)	531 (100.0)
FAS population	544 (100.0)	531 (100.0)
mITT population	397 (73.0)	388 (73.1)
mITT1 population	540 (99.3)	528 (99.4)
PP population	374 (68.8)	372 (70.1)
Safety population	540 (99.3)	528 (99.4)

Disposition Outcome	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Discontinued study drug[a]	23 (4.2)	21 (4.0)
Adverse event (AE)	10 (1.8)	5 (0.9)
Withdrawal by subject	7 (1.3)	11 (2.1)
No longer meets eligibility criteria	2 (0.4)	2 (0.4)
Other	4 (0.7)	3 (0.6)
Discontinued study[a]	20 (3.7)	21 (4.0)
Withdrawal by subject	12 (2.2)	17 (3.2)
Lost to follow-up	4 (0.7)	1 (0.2)
Death	0	1 (0.2)
Other	4 (0.7)	2 (0.4)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1488.
[a.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline and demographic characteristics are listed in Table 20. The two groups had similar distributions in these characteristics. All subjects were between 18 and 87 years of age. Approximately 52% of patients were female and 39% of subjects were from the United States.

Table 20. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-SR

Characteristic	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Sex		
Female	277 (50.9)	285 (53.7)
Male	267 (49.1)	246 (46.3)
Age, years		
Mean (SD)	41.7 (13.8)	42.4 (13.2)
Median (min, max)	40.0 (18.0, 87.0)	42.0 (18.0, 82.0)
Age group, years		
18 to 44	330 (60.7)	311 (58.6)
45 to 59	159 (29.2)	171 (32.2)
60 to 64	19 (3.5)	24 (4.5)
65 to 74	30 (5.5)	15 (2.8)
≥75	6 (1.1)	10 (1.9)
Race		
American Indian or Alaska Native	23 (4.2)	18 (3.4)
Asian	68 (12.5)	70 (13.2)
Black or African American	19 (3.5)	18 (3.4)
White	428 (78.7)	416 (78.3)
Unknown or Missing	6 (1.1)	9 (1.7)
Ethnicity		
Hispanic or Latino	235 (43.2)	225 (42.4)
Not Hispanic or Latino	306 (56.3)	301 (56.7)
Not Reported	3 (0.6)	5 (0.9)
Region		
United States	216 (39.7)	206 (38.8)
Europe	161 (29.6)	157 (29.6)
Rest of the World	167 (30.7)	168 (31.6)

Characteristic	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
BMI, kg/m^2		
Mean (SD)	26.4 (5.2)	26.6 (5.7)
Median (min, max)	24.9 (17.4, 58.8)	24.9 (14.2, 53.1)
Missing, n (%)	1 (0.2)	2 (0.4)
BMI group, kg/m^2		
<25	280 (51.5)	268 (50.5)
25 to <30	154 (28.3)	139 (26.2)
30 to <35	71 (13.1)	81 (15.3)
35 to <40	28 (5.1)	26 (4.9)
≥40	10 (1.8)	15 (2.8)
Missing	1 (0.2)	2 (0.4)
Duration since first symptom, days		
≤3	400 (73.5)	390 (73.4)
>3	144 (26.5)	141 (26.6)
Baseline serology status		
Negative	133 (24.4)	128 (24.1)
Positive	397 (73.0)	391 (73.6)
Unknown	14 (2.6)	12 (2.3)
Baseline Viral RNA shedding (NP samples, $\log_{10}$ copies/mL)		
Mean (SD)	5.19 (2.88)	4.85 (2.95)
Median (min, max)	6.20 (0, 9.47)	5.82 (0, 9.37)
Missing, n (%)	15 (2.8)	11 (2.1)
Vaccination Status		
Not Vaccinated	212 (39.0)	206 (38.8)
Vaccinated [a]	332 (61.0)	325 (61.2)
Baseline Risk factors		
No risk factor for severe COVID-19	221 (40.6)	211 (39.7)
With risk factor for severe COVID-19	323 (59.4)	320 (60.3)

Source: Reviewer's Analysis on ADSL datasets, excluding subjects from site 1281 and site 1488
[a] Among 657 (61.1%) fully vaccinated subjects, 636 (59.2%) subjects were fully vaccinated and at high risk for severe COVID-19.
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; NP, nasopharyngeal; RNA, r bonucleic acid; SD, standard deviation

Primary Efficacy Endpoint

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met. Table 21 displays analysis results for the time to sustained symptom alleviation endpoint in the mITT and mITT1 populations. No statistically significant difference between the two groups was observed in either analysis. Similar to EPIC-HR, there was high percentage of missing symptom diary data (15% treated subjects missed more than 25% symptom diary entries) in EPIC-SR (2021/pre-Omicron) (see Section 16.4.1 for more details).

Table 21. Time to Sustained Symptom Alleviation Through Day 28, EPIC-SR

Sustained Symptom Alleviation in mITT[a]	PAXLOVID N=397	Placebo N=388
Subjects with sustained symptom alleviation, n (%)	289 (72.8)	286 (73.7)
Median time to sustained symptom alleviation by Day 28 (95% CI)	12 (11, 13)	14 (12, 15)
Two-sided nominal p-value	0.4430	

Sustained Symptom Alleviation in mITT1[b]	PAXLOVID N=540	Placebo N=528
Subjects with sustained symptom alleviation, n (%)	388 (71.9)	382 (72.3)
Median time to sustained symptom alleviation by Day 28 (95% CI)	13 (11, 14)	14 (12, 15)
Two-sided nominal p-value	0.5150	

Source: Reviewer's analysis on ADTTESS dataset, excluding subjects from site 1281 and site 1488
Note: p-values calculated from log rank test
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Proportion of Subjects With COVID-19 Related-Hospitalization or Death From Any Cause Through Day 28

Table 22 displays analysis results for the prespecified secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. There was no statistically significant difference between the PAXLOVID group and the placebo group. However, a numerically lower hospitalization/death rate was observed in all randomized subjects in the PAXLOVID group. In addition, in an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed. None of the five hospitalized PAXLOVID subjects were admitted to the ICU. Three of the ten hospitalized placebo subjects were admitted to the ICU. There was one death reported in the trial, which was from the placebo group.

Table 22. Proportion of Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28, EPIC-SR

mITT1[a] Analysis	PAXLOVID N=540	Placebo N=528
Subjects with event, n (%)	5 (0.9)	10 (1.9)
COVID-19 hospitalization	5 (0.9)	10 (1.9)
Death	0	1 (0.2)
Estimated difference in proportion % (95% CI)[b]	-1.0 (-2.4, 0.5)	
Two-sided nominal p-value	0.1815	
Vaccinated High Risk Subgroup of mITT1[a] Analysis	**PAXLOVID N=317**	**Placebo N=314**
Subjects with event, n (%)	3 (0.9)	7 (2.2)
COVID-19 hospitalization	3 (0.9)	7 (2.2)
Death	0	1 (0.3)
Estimated difference in proportion % (95% CI)[b]	-1.3 (-3.3, 0.7)	
Two-sided nominal p-value	0.1970	

Source: Reviewer's analysis on ADTTE/ADSL datasets, excluding subjects from site 1281 and site 1488.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention.
[b.] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

Other Efficacy Endpoints

Results of efficacy endpoints including proportion of subjects with COVID-19 related medical visits and symptom diary-related efficacy endpoints in the mITT1 population are provided in Section 16.3. No statistically significant difference was observed between the two arms in any of these endpoints.

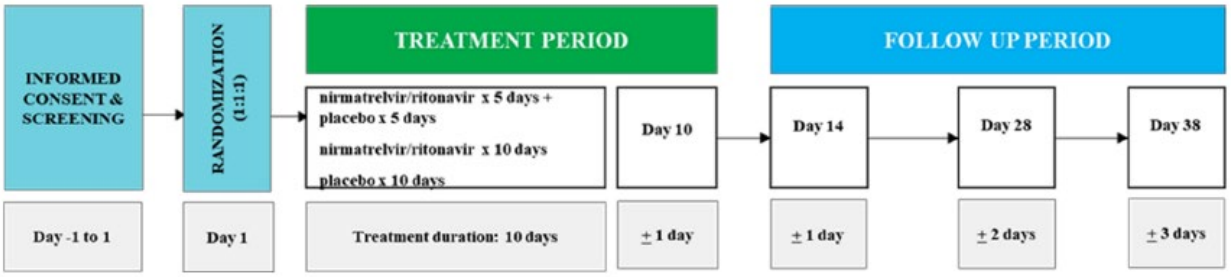
Analyses on viral RNA level related endpoints are provided in Section 6.3.2 and Section 6.3.3.

6.2.3. EPIC-PEP C4671006

6.2.3.1. Design, EPIC-PEP

EPIC-PEP was a randomized, double-blind, double-dummy, placebo-controlled Phase 2/3 global trial for post-exposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. Subjects with a negative screening SARS-CoV-2 rapid antigen test (RAT) result and who were asymptomatic household contacts of a symptomatic individual who recently tested positive for SARS-CoV-2 were enrolled. Eligible subjects were randomized 1:1:1 to receive PAXLOVID for 5 days (followed by placebo for 5 days), PAXLOVID for 10 days, or placebo for 10 days. Randomization was stratified by presence of risk factors associated with severe COVID-19 and geographic region. The total study duration was up to 42 days. The study schematic is summarized in Figure 6.

Figure 6. Study Design of EPIC-PEP



Source: EPIC-PEP Final Clinical Study Report, Figure 1.

The planned sample size was increased from 2660 to 2880 under protocol amendment 2 (January 25, 2022), based on external information on estimated relative risk reduction. The timing of planned interim efficacy analysis was changed from 45% subjects completing Day 14 assessments to 70% (with a minimum of 24 subjects having symptomatic infection in the mITT analysis set) to increase information collected on the Omicron variant.

An independent E-DMC reviewed unblinded safety data on an ongoing basis throughout the duration of the trial, and for a sentinel cohort of the first 150 subjects after completion through Day 10. The E-DMC conducted an interim analysis for efficacy and futility (with a sample size re-estimation) after approximately 70% of subjects completed the Day 14 assessments. The interim efficacy analysis concluded no change on sample size was needed. The trial failed the final primary efficacy analysis (see Section 6.2.3.4).

Due to data reliability concerns from two sites in EPIC-HR/EPIC-SR, data from the corresponding EPIC-PEP sites, Site 1281 and Site 1483, were also excluded from the review. Detailed discussion on data anomalies can be found in Section 6.3.1.

6.2.3.2. Eligibility Criteria, EPIC-PEP

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.3.

Inclusion Criteria

1. ≥18 years of age
2. Subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts (i.e., living in the same residence) of an individual who is symptomatic and recently tested positive for SARS-CoV-2 (i.e., index case: patient with symptomatic COVID-19)

Exclusion Criteria

1. History of SARS-CoV-2 infection as determined by a molecular test from any specimen collected within 6 months before or during the screening visit
2. Experiencing measured fever or other signs or symptoms consistent with COVID-19
3. Known medical history of active liver disease
4. CKD or have known moderate to severe renal impairment
5. Known HIV infection with viral load >400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment
6. Active cancer requiring treatment
7. Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening
8. Has received any SARS-CoV-2 vaccine (includes any level of vaccination) within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational post-exposure prophylaxis treatments through Day 38
9. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PAXLOVID
10. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PAXLOVID and during study treatment
11. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome)

Reference ID: 5179402

- eGFR <45 mL/min within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
- Absolute neutrophil count <1000/mm3

12. Females who are pregnant or breastfeeding

6.2.3.3. Statistical Analysis Plan, EPIC-PEP

The following analysis populations were included:

- **FAS**: All subjects randomly assigned to study intervention regardless of whether or not study intervention was administered
- **mITT**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline
- **mITT1**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline
- **mITT2**: All subjects randomly assigned to study intervention, who took at least 1 dose of study intervention, had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19
- **mITT3**: All subjects randomly assigned to study intervention who took at least 1 dose of study intervention
- **PP**: All subjects in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint
- **SAF**: All randomized subjects who received at least 1 dose of study intervention; subjects were analyzed according to the study intervention they received

The primary analysis was conducted using the mITT population.

The primary efficacy endpoint was the proportion of subjects with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. A symptomatic infection event through Day 14 was defined as having any reported symptoms consistent with COVID-19 (cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose, loss of smell, loss of taste) within 14 days of an RT-PCR or rapid antigen test-confirmed infection through Day 14.

There were two comparisons for the primary endpoint: 5-day regimen of PAXLOVID versus placebo and 10-day regimen of PAXLOVID versus placebo. Multiplicity adjustment for the primary endpoint were planned using Hochberg method. If the primary endpoint was significant for both treatment groups, the key secondary endpoint was to be tested at full alpha level using Hochberg method. If one treatment group was discontinued, sequential testing was to be performed in the remaining treatment groups in the order of the primary endpoint and the key secondary endpoint. The key secondary efficacy endpoint was the proportion of subjects with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adult subjects who had a negative RT-PCR result at baseline and who were at increased risk of severe COVID-19.

The trial failed the primary efficacy analysis (see Section 6.2.3.4).

6.2.3.4. Results of Analyses, EPIC-PEP

After excluding Site 1281 and Site 1483, 2880 subjects were screened and 2736 were randomized. Results of EPIC-PEP analyses are summarized in this section.

Table 23. Subject Disposition, EPIC-PEP

Disposition Outcome	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Subjects randomized			
FAS population	921 (100.0)	917 (100.0)	898 (100.0)
mITT population	844 (91.6)	830 (90.5)	840 (93.5)
mITT1 population	38 (4.1)	48 (5.2)	29 (3.2)
mITT2 population	627 (68.1)	605 (66.0)	606 (67.5)
mITT3 population	889 (96.5)	887 (96.7)	873 (97.2)
PP population	724 (78.6)	723 (78.8)	720 (80.2)
Safety population[a]	912	911	898
Discontinued study drug[b]	54 (5.9)	58 (6.3)	45 (5.0)
Adverse event (AE)	10 (1.1)	11 (1.2)	14 (1.6)
Withdrawal by subject	19 (2.1)	25 (2.7)	17 (1.9)
No longer meets eligibility criteria	3 (0.3)	2 (0.2)	1 (0.1)
Medication error without associated adverse event	7 (0.8)	10 (1.1)	9 (1.0)
Non-compliance with study drug	0	0	1 (0.1)
Pregnancy	0	0	1 (0.1)
Other	15 (1.6)	10 (1.1)	2 (0.2)
Discontinued study[b]	44 (4.8)	53 (5.8)	35 (3.9)
Withdrawal by subject	25 (2.7)	36 (3.9)	23 (2.6)
Lost to follow-up	9 (1.0)	11 (1.2)	7 (0.8)
Other	10 (1.1)	6 (0.7)	5 (0.6)

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483.
[a.] Based on treatment actually received. One subject randomized to the PAXLOVID 5-day group received placebo.
[b.] Percentages are based on number of randomized subjects.
Abbreviations: FAS, full analysis set, mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; PP, per-protocol

Baseline and demographic characteristics are listed in Table 24. The two groups had similar distributions in these characteristics. All subjects were between 18 and 91 years of age. Approximately 54% of subjects were female and 72% of subjects were from the United States.

Table 24. Baseline Demographic and Clinical Characteristics, Full Analysis Set, EPIC-PEP

Characteristic	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Sex			
Female	502 (54.5)	479 (52.2)	474 (52.8)
Male	419 (45.5)	438 (47.8)	424 (47.2)
Age, years			
Mean (SD)	43.9 (14.9)	42.8 (15.0)	42.4 (14.4)
Median (min, max)	43.0 (18.0, 89.0)	41.0 (18.0, 91.0)	41.0 (18.0, 87.0)

Characteristic	PAXLOVID 5-Day N=921 n (%)	PAXLOVID 10-Day N=917 n (%)	Placebo N=898 n (%)
Age group, years			
18 to 44	479 (52.0)	530 (57.8)	509 (56.7)
45 to 59	301 (32.7)	251 (27.4)	279 (31.1)
60 to 64	62 (6.7)	53 (5.8)	44 (4.9)
65 to 74	50 (5.4)	58 (6.3)	49 (5.5)
≥75	29 (3.1)	25 (2.7)	17 (1.9)
Race			
American Indian or Alaska Native	58 (6.3)	52 (5.7)	49 (5.5)
Asian	8 (0.9)	15 (1.6)	11 (1.2)
Black or African American	139 (15.1)	136 (14.8)	132 (14.7)
White	714 (77.5)	711 (77.5)	704 (78.4)
Multiple	1 (0.1)	1 (0.1)	1 (0.1)
Unknown or Missing	1 (0.1)	2 (0.2)	1 (0.1)
Ethnicity			
Hispanic or Latino	664 (72.1)	642 (70.0)	643 (71.6)
Not Hispanic or Latino	257 (27.9)	275 (30.0)	255 (28.4)
Region			
United States	642 (69.7)	639 (69.7)	621 (69.2)
Europe	110 (11.9)	114 (12.4)	112 (12.5)
Rest of the World	169 (18.3)	164 (17.9)	165 (18.4)
BMI, kg/m^2			
Mean (SD)	28.0 (5.8)	27.7 (5.5)	28.0 (5.9)
Median (min, max)	27.2 (15.7, 60.1)	27.1 (17.8, 65.0)	27.1 (16.0, 69.1)
BMI group, kg/m^2			
<25	339 (36.8)	356 (38.8)	335 (37.3)
25 to <30	291 (31.6)	276 (30.1)	289 (32.2)
30 to <35	196 (21.3)	212 (23.1)	183 (20.4)
35 to <40	66 (7.2)	49 (5.3)	57 (6.3)
≥40	29 (3.1)	24 (2.6)	34 (3.8)
Baseline serology status			
Negative	75 (8.1)	86 (9.4)	69 (7.7)
Positive	838 (91.0)	820 (89.4)	823 (91.6)
Unknown	8 (0.9)	11 (1.2)	6 (0.7)
Baseline RT-PCR status			
Negative	872 (94.7)	855 (93.2)	864 (96.2)
Positive	38 (4.1)	48 (5.2)	29 (3.2)
Missing	11 (1.2)	14 (1.5)	5 (0.6)
Vaccination Status			
Subjects DID receive at least one dose of COVID-19 vaccine	118 (12.8)	116 (12.6)	121 (13.5)
Subjects DID NOT receive at least one dose of COVID-19 vaccine	803 (87.2)	801 (87.4)	777 (86.5)
Baseline Risk factor			
No risk factor for severe COVID-19	246 (26.7)	253 (27.6)	251 (28.0)
With risk factor for severe COVID-19	675 (73.3)	664 (72.4)	647 (72.0)

Source: Reviewer's Analysis on ADSL dataset, excluding subjects from site 1281 and site 1483
Abbreviations: BMI, body mass index; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SD, standard deviation

Efficacy Analyses

The study failed the primary efficacy analysis. Table 25 displays analysis results for the endpoint of proportion of subjects with symptomatic infection through Day 14 in the mITT (primary endpoint), mITT1, mITT2 (key secondary endpoint) and mITT3 populations. There was no statistically significant difference in any analysis. Numerically lower infection rates were observed in both PAXLOVID groups compared to placebo in the mITT, mITT2 and mITT3 populations.

Table 25. Proportion of Subjects With Symptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14, EPIC-PEP

Symptomatic Infection in mITT[a]	**PAXLOVID5-Day N=844**	**PAXLOVID 10-Day N=830**	**Placebo N=840**
Subjects with event, n (%)	22 (2.6)	20 (2.4)	33 (3.9)
Estimated risk ratio vs. placebo	0.70	0.65	
Two-sided nominal p-value	0.1722	0.1163	
Symptomatic Infection in mITT2[b]	**PAXLOVID 5-Day N=627**	**PAXLOVID 10-Day N=605**	**Placebo N=606**
Subjects with event, n (%)	18 (2.9)	16 (2.6)	21 (3.5)
Estimated risk ratio vs. placebo	0.88	0.81	
Two-sided nominal p-value	0.6766	0.5070	
Symptomatic Infection in mITT1[c]	**PAXLOVID 5-Day N=38**	**PAXLOVID 10-Day N=48**	**Placebo N=29**
Subjects with event, n (%)	11 (28.9)	22 (45.8)	11 (37.9)
Estimated risk ratio vs. placebo	0.75	1.24	
Two-sided nominal p-value	0.4126	0.4273	
Symptomatic Infection in mITT3[d]	**PAXLOVID 5-Day N=889**	**PAXLOVID 10-Day N=887**	**Placebo N=873**
Subjects with event, n (%)	33 (3.7)	43 (4.8)	46 (5.3)
Estimated risk ratio vs. placebo	0.73	0.95	
Two-sided nominal p-value	0.1333	0.8088	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483
Note: Estimated risk ratios and p-values are calculated from GEE model with a log link function and fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19 (except mITT2). The compound symmetry variance-covariance structure was used to account for the correlation among the subjects associated with the same index case.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline.
[b.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19.
[c.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline.
[d.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative, positive, or missing RT-PCR result at baseline.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 26 displays analysis results for the endpoint of proportion of subjects with asymptomatic infection through Day 14 in the mITT population. There was no statistically significant difference in either analysis. Numerically lower asymptomatic infection rates were observed in both PAXLOVID groups compared to placebo.

Table 26. Proportion of Subjects With Asymptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14, EPIC-PEP

Asymptomatic Infection in mITT[a]	PAXLOVID 5-Day N=844	PAXLOVID 10-Day N=830	Placebo N=840
Subjects with event, n (%)	17 (2.0)	16 (1.9)	26 (3.1)
Estimated risk ratio vs. placebo	0.67	0.63	
Two-sided nominal p-value	0.1869	0.1221	

Source: Reviewer's analysis on ADSL dataset, excluding subjects from site 1281 and site 1483.
Note: Estimated risk rations and p-values are calculated from GEE model with fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19. The compound symmetry variance-covariance structure was used to account for the correlation among the subjects associated with the same index case.
[a.] All subjects randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; GEE, generalized estimating equations; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; RAT, rapid antigen test; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Among subjects who had a negative RT-PCR result at baseline (mITT population), RT-PCR or rapid antigen test (RAT) confirmed SARS-CoV-2 infection through Day 14, regardless of the presence or absence of symptoms, was reported for 39 (4.6%) and 36 (4.3%) subjects in the PAXLOVID 5-day and 10-day groups, respectively, fewer than the 59 (7.0%) subjects in the placebo group.

Each treatment group had one COVID-19 related hospitalization event. The two subjects from PAXLOVID groups with hospitalization events had positive RT-PCR results at baseline (not in the mITT population). The subject from the placebo group with a hospitalization event had a negative RT-PCR result at baseline (in the mITT population). No deaths were reported in this trial.

6.3. Key Efficacy Review Issues

6.3.1. Data Reliability Issues at Specific Clinical Trial Sites

Issue

Are the clinical EPIC-HR and EPIC-SR data reliable for regulatory decision-making in the context of viral RNA and symptom data anomalies identified at certain clinical trial sites?

Background

Both EPIC-HR and EPIC-SR were global trials that enrolled subjects across numerous clinical study sites in up to 19 countries across 5 continents, with subjects enrolled at 191 sites in EPIC-HR and 195 sites in EPIC-SR.

During the conduct of the NDA review, the review team identified unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects at selected study sites in EPIC-HR and EPIC-SR [EPIC-HR 1274/EPIC-SR 1281 (Principal investigator [PI]: Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria)]. These observations triggered additional site inspections and in-depth investigations of all study data and sites from EPIC-HR and EPIC-

SR in order to determine if there were data reliability issues and, if so, if these were limited to specific study sites or were due to a central issue.

In addition, one study site (PI: Hernandez, Sunrise, FL, United States) that enrolled subjects for EPIC-HR (Site 1470), EPIC-SR (Site 1488), and EPIC-PEP (Site 1483), did not have the unusual data patterns noted above but was selected for a site inspection for cause based on reports of GCP noncompliance[1].

Assessment

EPIC-HR 1274 and EPIC-SR 1281 (PI: Martinez, Cutler Bay, FL, United States)

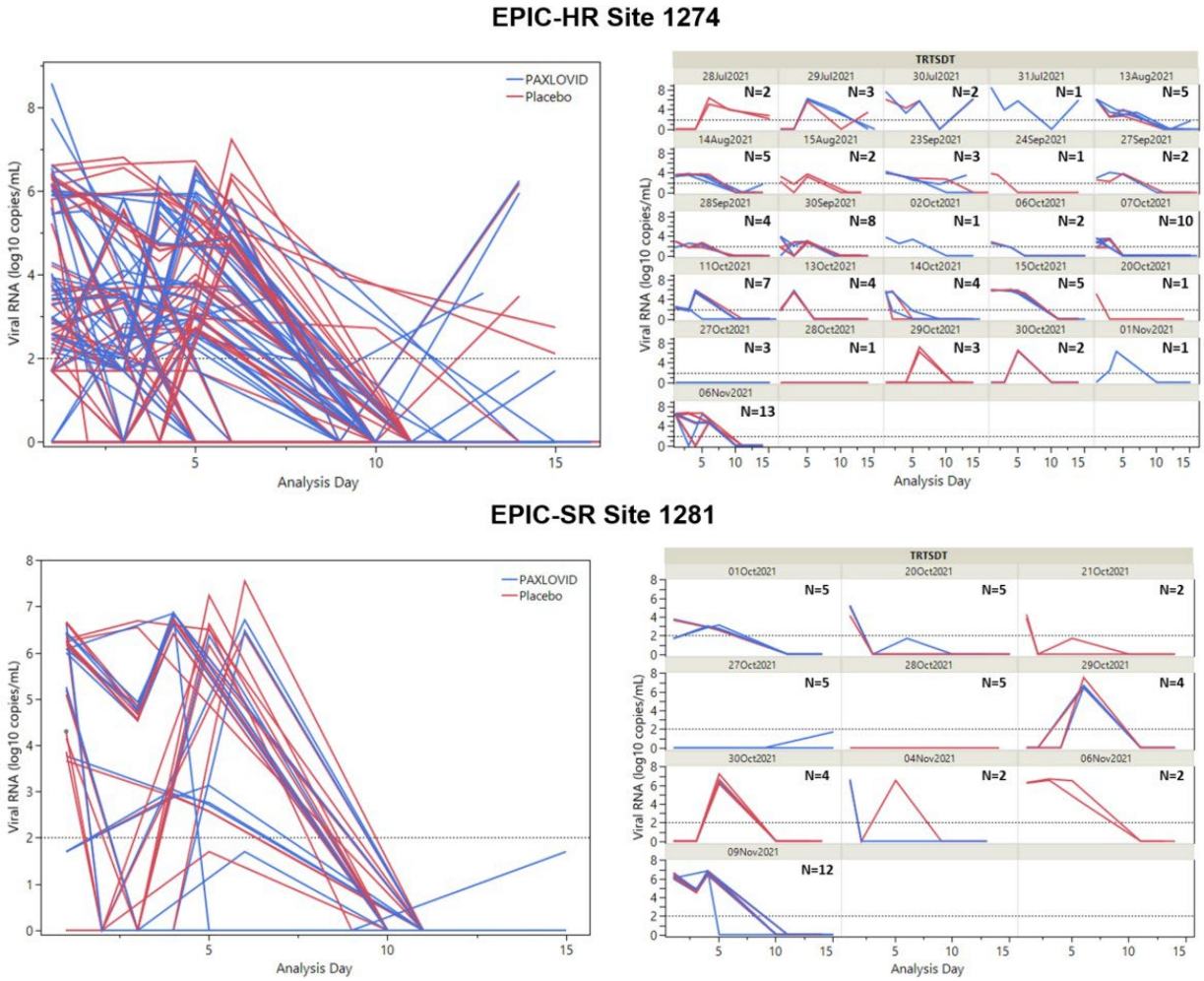
Viral RNA and Sequencing Data Anomalies

EPIC-HR 1274 was the only study site in EPIC-HR from which markedly unusual patterns of viral RNA levels and viral sequences in nasopharyngeal (NP) samples among subjects were observed, with similar unusual patterns observed from subjects enrolled at this same location in EPIC-SR (EPIC-SR 1281). The unusual viral RNA patterns were characterized by a high degree of overlapping and often implausible trends in viral RNA levels over time in different subjects at the same site, which in many cases were associated with similar timing of treatment initiation (Figure 7). For example, in EPIC-HR 1274, four different subjects who all started treatment on October 13, 2021, (2 received PAXLOVID, 2 received placebo) had a similar major spike in viral RNA levels between the Baseline and the Day 3 visits, and in all subjects viral RNA declined to undetected levels at all subsequent visits. As another example from EPIC-HR 1274, five subjects who started treatment on October 15, 2021, (3 received PAXLOVID, 2 received placebo) all had highly similar viral RNA levels which had a relatively delayed decline over time.

The overlapping viral RNA patterns within this site extended between both trials. For example, 12 different subjects across both trials who initiated treatment on October 29, 2021, or October 30, 2021, had highly similar patterns of viral RNA over time, with viral RNA levels of 6.2-7.6 $\log_{10}$ copies in the Day 5 visit window, and viral RNA levels reported as undetected at all other study visits, including baseline. These and other viral RNA patterns from this site are highly implausible and raised concerns about virology data quality or data integrity.

[1] The Applicant investigated this site due to an October 1, 2021, report (b) (6) which stated that study procedures were conducted at a facility which was not identified on the FDA form 1572 for a subset of study subjects in EPIC-HR and EPIC-SR and that the principal investigator was not always on site to see study subjects during their visits. The Applicant conducted an on-site audit from October 6 to 8, 2021, and found that the allegation regarding the use of another facility could not be ruled out, that the principal investigator provided inadequate oversight, and that there were additional instances of GCP non-compliance. Consequently, the Applicant closed this site, censored the data from subjects who had completed the trial at this site, and transferred active subjects enrolled at this site to nearby study sites to complete the trial.

Figure 7. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Martinez)



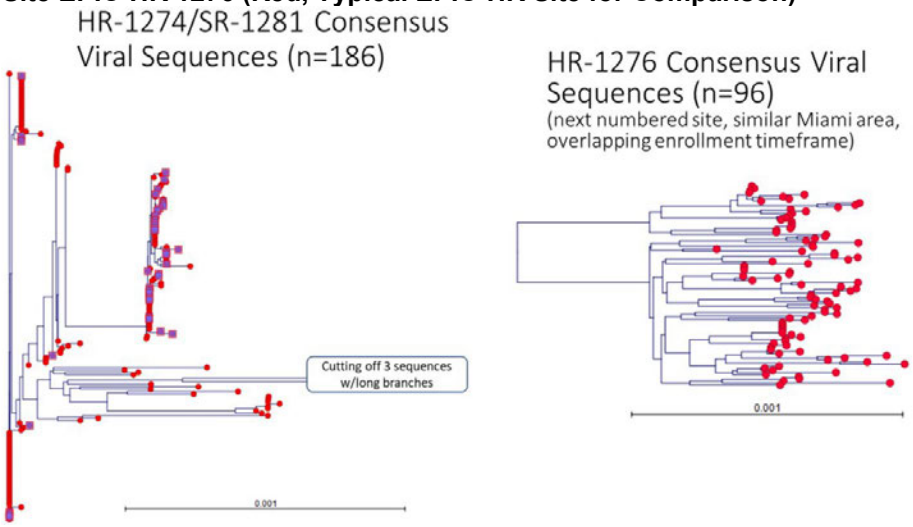
Source: FDA analysis of ADSL and ADMC datasets.
Note: Each line represents viral RNA levels from an individual subject. Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: log, logarithm; LLOQ, lower limit of quantitation; N, number of subjects in treatment group; NP, nasopharyngeal; PI, principal investigator; qRT-PCR, quantitative, real-time, reverse transcription-polymerase chain reaction; RNA, r bonucleic acid; TRTSDT, treatment start date

The same viral RNA samples used for qRT-PCR analyses were subjected to next-generation sequencing (NGS) analyses to support resistance analyses and identification of SARS-CoV-2 variants. Following the observations of overlapping viral RNA patterns noted above, extensive analyses of viral sequences were conducted by the Applicant and FDA to assess for unusual patterns of genetic clustering, which could indicate flawed or improper sample handling or processing. These analyses were conducted on consensus nucleotide sequences spanning the entire ~30 kb SARS-CoV-2 genome.

As shown in Figure 8, phylogenetic analyses of viral consensus nucleotide sequences indicated extensive genetic clustering of numerous viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site, with many sequences having minimal to nonexistent branch lengths indicating nearly or completely identical viral nucleotide sequences. These results contrast with data from other sites, for example EPIC-HR site 1276 (Figure 8), which typically show longer branch lengths and minimal clustering of highly similar viral sequences other than

those representing different visits from the same subject. These analyses confirmed similar observations from phylogenetic analyses conducted by the Applicant. This extent of viral genetic conservation across different subjects is implausible and strongly indicates flawed NP swab sample collection, handling, or processing from this site.

Figure 8. Phylogenetic Analysis of Viral Sequences From Site EPIC-HR 1274 (Red)/EPIC-SR 1281 (Purple), and Site EPIC-HR 1276 (Red, Typical EPIC-HR Site for Comparison)

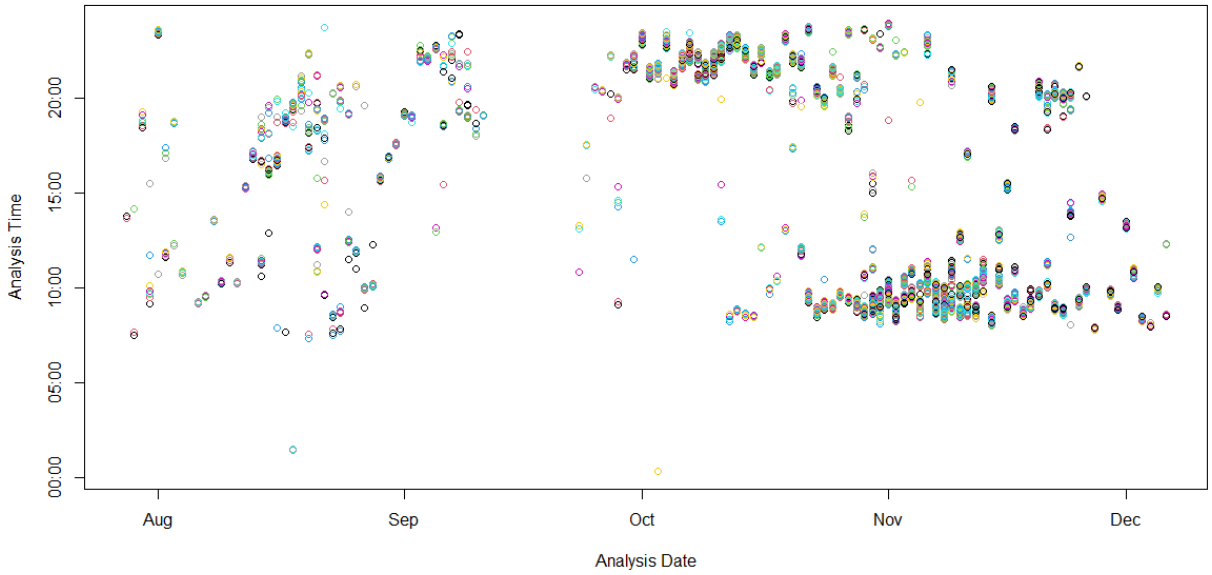


Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.
Abbreviations: n, number of sequences in specified group

Symptom Data Reporting Time Anomalies

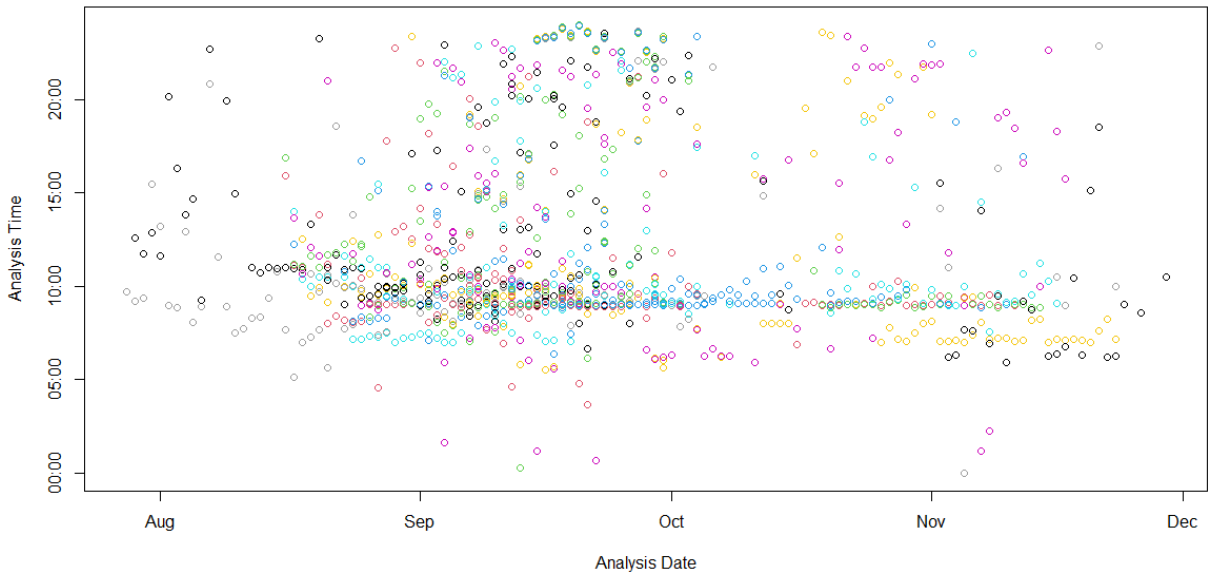
Unusual symptom data reporting time clusters were also observed at site EPIC-HR 1274/EPIC-SR 1281. As shown in Figure 9 for site EPIC-HR 1274/EPIC-SR 1281, many groups of subjects were observed to have similar daily symptom reporting time stamps, and the average time of those similar time stamps changed daily. Those groups of subjects with similar symptom reporting time stamps coincide with the groups of subjects sharing overlapping viral RNA patterns. For comparison, Figure 10 shows symptom reporting time from site EPIC-HR 1276/EPIC-SR 1282, which is similar in location and enrollment timeframe to site EPIC-HR 1274/EPIC-SR 1281. At site EPIC-HR 1276/EPIC-SR 1282, randomness was observed in symptom reporting time stamps, which reflects between-subject differences in symptom reporting time. The majority of symptom reporting time centered around 10:00, which is consistent with the recommendation of completing symptom eDiary at approximately the same time each day.

Figure 9. Symptom Data Reporting Time at Site HR1274/SR1281



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 10. Symptom Data Reporting Time at Site HR1276/SR1282

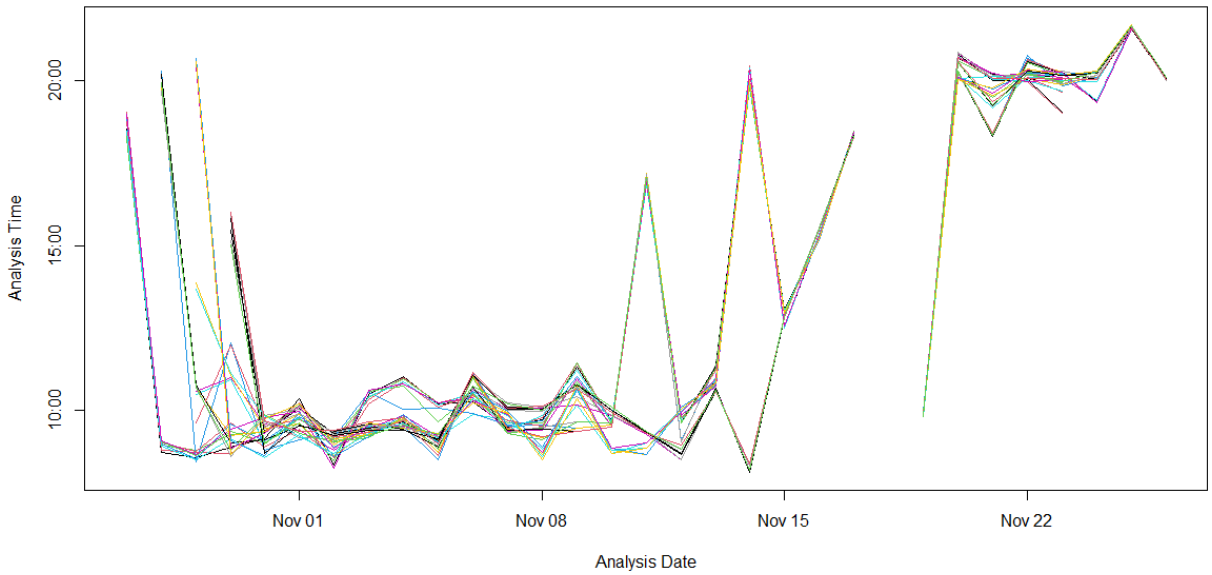


Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 11 and Figure 12 show symptom data reporting time of subjects from EPIC-HR 1274/EPIC-SR 1281 and EPIC-HR 1276/EPIC-SR 1282 within specific treatment initiation time periods. EPIC-HR 1274/EPIC-SR 1281 subjects in Figure 11 initiated treatment between October 27, 2021, and October 30, 2021. Two notable patterns were identified: (1) all subjects (n=9) from EPIC-HR 1274 and all subjects (n=18) from EPIC-SR 1281 did not report symptom data on November 18, 2021, and (2) on the preceding and following days, all 27 subjects had symptom data reported within a narrow timeframe (between 18:17 and 18:29 on November 17, 2021, and between 9:49 and 9:59 on November 19, 2021). For comparison, Figure 12 shows

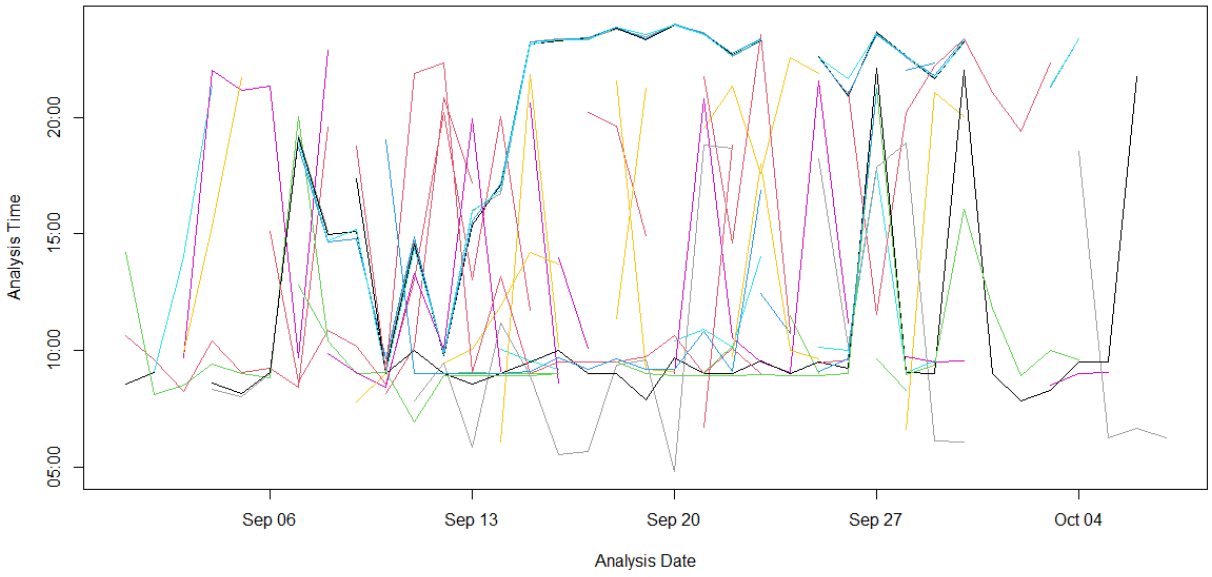
reporting time of subjects from EPIC-HR 1276/EPIC-SR 1282 who initiated treatment between September 1, 2021, and September 10, 2021 (20 subjects in total). Randomness was observed in symptom reporting time stamps in this example.

Figure 11. Symptom Data Reporting Time at Site HR1274/SR1281 for Subjects With Treatment Start Date Between October 27, 2021, and October 30, 2021



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

Figure 12. Symptom Data Reporting Time at Site HR1276/SR1282 for Subjects With Treatment Start Date Between September 1, 2021, and September 10, 2021



Source: Reviewer's Analysis on EPIC-HR and EPIC-SR ADSO datasets.

The Applicant conducted analyses on the following two key risk indicators (KRIs) using the software application, CluePoints, to assess potential data entry anomalies:

- Time between subsequent data entry times for subjects entering eDiary data on the same date within the same site (Symptom eDiary Data Entry to Subsequent Data Entry Gap [SDOOG]).
- Time between the data save time of the previous entry and data entry time for the next entry for subjects entering eDiary data on the same date within the same site (Symptom eDiary Data Saved to Subsequent Data Entry Gap [SDOSG]).

In the CluePoints analyses combining EPIC-HR and EPIC-SR 2021 data, grouped by investigator, site HR 1274/SR 1281 was identified as high risk for SDOOG and medium risk for SDOSG, which further supports the FDA analysis findings.

The Applicant also reported that all subjects from site EPIC-HR 1274/EPIC-SR 1281 were using the same PIN code, 1274, for eDiary reporting. Note that subjects were supposed to have independent PIN codes for confidentiality and site staff should not be able to have access to eDiary data entries.

Inspection Findings

EPIC-HR 1274 had already been chosen as one of four clinical sites for routine inspection based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results. After the above data anomalies were noted in the viral RNA levels, viral sequencing results, and daily clinical symptom reporting times from EPIC-HR 1274/EPIC-SR 1281, the planned inspection was expanded to include EPIC-SR 1281 (Martinez, Cutler Bay, FL, United States). The Office of Scientific Investigations noted the following key findings from the inspection of EPIC-HR 1274/EPIC-SR 1281:

- (b) (7)(A)

- An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, multiple subjects were instructed to change their eDiary PIN code to one provided by the study staff. Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- There were no hospitalizations or deaths reported for either EPIC-HR 1274 or EPIC-SR 1281.

Site EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria, 2022 Enrollment Period)

Viral RNA and Sequencing Data Anomalies

Unusual patterns of overlapping viral RNA levels over time, similar to what was observed for EPIC-HR 1274/ EPIC-SR 1281, were also observed in data from EPIC-SR 1157 (PI:

Medzhidiev, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Bulgaria) specifically during the 2022 (Omicron) enrollment period.

Analyses conducted by the Applicant and FDA also found extensive clustering of viral sequences from EPIC-SR 1157, much like the observations from EPIC-HR 1274/EPIC-SR 1281. Clustering of viral sequences from EPIC-SR 1197 was not as obvious as observed for the other sites, but for subjects who enrolled in the 2022 period (among whom anomalous viral RNA patterns were observed) there was evidence of clustering of viral sequences with short or no branch lengths.

The viral RNA and sequencing data anomalies from these sites are described in detail in review Section 18.5.

Symptom Data Reporting Time Anomalies

All five subjects from EPIC-SR 1197 with treatment start date of April 18, 2022, had no symptom data on 03May 2022. No other abnormal symptom data entry time pattern was identified.

Inspection Findings

Though not initially planned for routine clinical site inspections, both EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria) and EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria) were added as inspection sites based on the unusual patterns of viral RNA levels and viral sequencing results along with eDiary symptom data collection anomalies. In addition, EPIC-HR 1193 was added for inspection because it had the same principal investigator as EPIC-SR 1197 (Haytova, Vratsa, Bulgaria). The Office of Scientific Investigations noted key findings from the inspections listed below.

EPIC-SR 1157 (PI: Medzhidiev, Sofia, Bulgaria)

- An FDA Form 483 was issued stating that during the conduct of EPIC-SR, the clinical investigator did not ensure that each subject created a new device PIN code that remained confidential to the subject only. Instead, subjects were instructed to use PIN codes that were easy to remember, such as their birth dates, which were readily available to the site. Records revealed that 48 of 49 enrolled subjects used their birth year as their new PIN code.
- Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- There were no hospitalizations or deaths reported.

EPIC-HR 1193/EPIC-SR 1197 (PI: Haytova, Vratsa, Bulgaria)

- An FDA Form 483 was issued stating that during the conduct of EPIC-SR and EPIC-HR, the clinical investigator did not follow the Site User Guide. Specifically, the Site User Guide for the electronic patient reported outcome (ePRO) application used in the study to collect electronic diaries states “The participant should not share their PIN code with anyone, not even with study staff. The new PIN code must remain confidential, with only the participant knowing the PIN code.” However, when assisting subjects to download and activate the application, the investigator’s site staff provided suggestions in a manner that caused the

subjects in the studies to create nonconfidential PIN codes. The investigator's site staff gave examples of easily memorable numbers to use for a PIN code, including birth year and specific numbers such as "2323."

- Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the eDiaries.
- For EPIC-HR 1193, the occurrence of COVID-19 related hospitalizations and death from any cause were verified against the data line listings provided by the Applicant for all 59 randomized subjects (there were no hospitalizations or deaths in EPIC-SR 1197).

EPIC-HR 1470 (PI: Hernandez, Sunrise, FL, United States)

Viral RNA and Sequencing Data Anomalies

None identified.

Symptom Reporting Data Anomalies

None identified.

Inspection Findings

EPIC-HR 1470 was selected for inspection due to a complaint and subsequent site closure by the Applicant for GCP noncompliance, as described in the background above; this investigator (Hernandez, Sunrise, FL, United States) also had a site for EPIC-SR (1488) that was not included in the inspection. The Office of Scientific Investigations noted the following key findings from this inspection:

- An FDA Form 483 was issued stating that five of 23 subjects did not meet an inclusion criterion, or met an exclusion criterion, but were screened, enrolled, randomized, and received investigational product.
- The Applicant's previous investigation had found GCP non-compliance at this site (please see the background section for more details), and consequently this site and the corresponding EPIC-SR site (1488) were closed during the trial conduct period.
- Based on the totality of findings from the FDA inspection and the Applicant's inspection of this site, the review team had concerns about the reliability of the clinical data generated at this site. The Applicant had already censored data from the subjects who were enrolled and completed all study assessments (n=2 for EPIC-HR 1470, n=1 for EPIC-SR 1488). However, it was noted by the Office of Scientific Investigations that subjects who were enrolled and who completed Day 28 visits at this site were not censored and were listed in the datasets with the site they were later transferred to for long-term follow-up (n=36 for EPIC-HR 1470, n=30 for EPIC-SR 1488). Notably, most data for the efficacy and safety endpoints were collected by Day 28.

Other EPIC-HR and EPIC-SR Clinical Sites

Viral RNA and Sequencing Data Anomalies

Numerous additional analyses were conducted by the Applicant and FDA to assess for viral RNA or sequencing anomalies across all study sites in EPIC-HR and EPIC-SR, and ultimately to ensure reliability of these data from other study sites. These included systematic analyses of viral RNA levels for evidence of concordant patterns over time for different subjects at the same site, and both phylogenetic and BLAST (Basic Local Alignment Search Tool) analyses of viral sequences to identify any additional sites with unusually high frequencies of highly similar or identical viral nucleotide sequences. Also, analyses were conducted to identify sites with high frequencies of subjects with low or undetected viral RNA levels.

Overall, these systematic analyses confirmed the observations of overlapping viral RNA patterns and clustering of viral sequences noted above for sites EPIC-HR 1274/EPIC-SR 1281 (PI: Gonzalez/Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria). No other sites with similar patterns were identified. Additional sites were identified with high frequencies of subjects with low or undetected viral RNA at baseline, which could be explained by the immunologic characteristics of the population or characteristics of the virus circulating at the time, as these sites were clustered geographically, and most subjects were seropositive for SARS-CoV-2 at baseline.

See Section 18.5, for additional details, investigations, and discussion regarding the viral RNA and sequencing data anomalies observed at certain study sites in EPIC-HR and EPIC-SR.

Symptom Data Reporting Time Anomalies

Additional analyses were conducted to evaluate EPIC-HR and EPIC-SR sites with observable time stamp clusters, sites identified as medium risk in the Applicant's CluePoints analyses, and sites with high percentage of common PIN codes. These sites did not have similar viral RNA data issues as observed in EPIC-HR 1274/EPIC-SR 1281. Additional sensitivity analyses were conducted on the EPIC-HR primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28, to evaluate the potential impact of removing those sites. The sensitivity analyses showed consistent results with the results in Section 6.2.1. See Section 16.1 for details on the additional analyses. To evaluate the potential impact of these sites on symptom rebound analyses, additional analyses were conducted in Section 16.4, with consistent conclusions as those in Section 6.3.6.

Inspection Findings

Three additional sites were chosen for routine inspection based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results: EPIC-HR 1108 (PI: Igbinadolor, Monroe, NC, United States); EPIC-HR 1158 (PI: Mitreva, Samokov, Bulgaria); and EPIC-HR 1097 (PI: Simova, Pleven, Bulgaria). No issues were identified at these sites. The occurrence of COVID-19 related hospitalizations and death from any cause at Day 28 were verifiable at all three sites.

Assessments for Anomalies in Other Types of Data

Other EPIC-HR and EPIC-SR data (AEs, vital signs, safety laboratory findings, electrocardiograms (ECGs), and pharmacokinetic data) were analyzed to look for unusual site-specific patterns. No overtly suspicious site-specific patterns were detected from these other data sources. Furthermore, CluePoints analyses done by FDA looking at multiple data elements including laboratory values did not uncover any site-specific atypical results that could not be explained by geographic differences and normal variation.

Conclusion

The extensive analyses summarized above indicate that viral RNA shedding data, viral sequencing data, and certain symptom reporting data from sites EPIC-HR 1274/EPIC-SR 1281 (PI: Martinez), EPIC-SR 1157 (PI: Medzhidiev, Bulgaria) and EPIC-SR 1197 (2022 enrollment period; PI: Haytova, Bulgaria) are highly unusual and implausible, raising concerns about data quality or reliability from these sites. Given the concerning data patterns, the review team determined that these sites should be excluded from all key efficacy, safety, and virology analyses. Note that data from EPIC-SR collected during the 2022/Omicron period were not used for primary efficacy and safety analyses; these data contributed to analyses of viral RNA shedding, drug resistance, and COVID-19 rebound.

Likewise, given that the reliability of data from site EPIC-HR 1470/EPIC-SR 1488 was in question due to the identified GCP noncompliance, and because data for the main efficacy and safety analyses were collected by Day 28, the review team determined that data from all subjects enrolled at this site should also be excluded from the key analyses.

There is no indication that any of the data anomalies or clinical trial oversight concerns were in any manner related to specific treatment assignment, and therefore, data from these sites do not contribute towards any potentially flawed efficacy or safety conclusions regarding PAXLOVID versus placebo. All conclusions on overall efficacy and safety, viral RNA shedding and resistance, and viral and symptomatic rebound remain unchanged regardless of whether these study sites are censored.

In conclusion, the following sites/subjects were excluded from all key efficacy, safety, and virology analyses of the EPIC-HR and EPIC-SR trials that are included in this review:

- EPIC-HR: Sites 1274 (PI: Martinez, N=95 treated) and 1470 (including subjects [IDs that start with 1470] who transferred to 1276, N=38 treated)
- EPIC-SR Pre-Omicron, data through December 19, 2021 cut-off: Sites 1281 (PI: Martinez, N=46 treated), and 1488 (including subjects [IDs which start with 1488] who transferred to site 1282, N=31 treated)
- EPIC-SR Post-Omicron, 2022 data: Sites 1157 (PI: Medzhidiev, N=47 treated) and 1197 (PI: Haytova, 2022 enrollees only, N=18 treated)
- Total N excluded: 275 treated (133 in EPIC-HR, 142 in EPIC-SR; 137 PAXLOVID-treated, 138 placebo-treated)

The exclusion of these sites required resubmission of key analyses by the Applicant, and confirmatory analyses by the FDA, which constituted a major amendment and extended the Prescription Drug User Fee Act (PDUFA) review clock.

Given the concerns on data reliability of sites EPIC-HR 1274/EPIC-SR 1281 and EPIC-HR 1470/EPIC-SR 1488, data of the corresponding sites in EPIC-PEP, EPIC-PEP 1281 (EPIC-HR 1274/EPIC-SR 1281) and EPIC-PEP 1483 (EPIC-HR 1470/EPIC-SR 1488), were also excluded from the review of EPIC-PEP.

6.3.2. Efficacy in High-Risk Adults Who Are Vaccinated Against COVID-19 or Previously Infected With SARS-CoV-2

Issue

Is the benefit-risk assessment favorable for PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk individuals who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2?

Background

The proposed PAXLOVID indication is for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or prior SARS-CoV-2 infection. However, EPIC-HR, the pivotal trial which demonstrated an 86% relative risk reduction (RRR) for PAXLOVID in the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 (mITT1 population), enrolled high-risk adults who had not received any dose of a COVID-19 vaccine and who had not had a prior confirmed SARS-CoV-2 infection. Because COVID-19 vaccination is known to reduce the risk of severe disease (CDC 2023b), the relevance of the benefit with PAXLOVID observed in EPIC-HR to high-risk adults with pre-existing SARS-CoV-2 immunity was an important review issue.

Currently, the overwhelming majority of adults in the United States have either received one or more COVID-19 vaccine doses or previously been infected with SARS-CoV-2. As of March 1, 2023, 92% of the total U.S. population ≥18 years of age, and 95% of the U.S. population ≥65 years of age, had received at least one COVID-19 vaccine dose (CDC 2023b). In addition, 79% of the total U.S. population ≥18 years of age, and 94% of the population ≥65 years of age, had completed a COVID-19 primary vaccination series. Furthermore, the results from EPIC-PEP, which enrolled from September 9, 2021, to March 1, 2022 (a later enrollment period than for EPIC-HR), indicate that even unvaccinated adults were likely to be SARS-CoV-2 seropositive by 2022, presumably from prior infection. In EPIC-PEP, which enrolled adults with negative screening SARS-CoV-2 rapid antigen test results and who were asymptomatic household contacts of individuals with COVID-19, only 12% of subjects reported receiving at least one COVID-19 vaccine dose, but 91% were SARS-CoV-2 seropositive at baseline.

Assessment

Methods

In order to assess the benefit and risk of PAXLOVID treatment in high-risk adults who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2, EPIC-HR and EPIC-SR efficacy and safety data were analyzed as described in the sections below. Unless otherwise noted, in both trials the mITT1 population (treated within 5 days of symptom onset

and not expected to receive a COVID-19 mAb treatment) was used as this population is most consistent with the indication proposed by the Applicant for PAXLOVID labeling.

Three different populations were identified from EPIC-HR and EPIC-SR, the two trials evaluating PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. All subjects in these three populations had at least one risk factor that put them at high risk for progression to severe disease:

(1) The Vaccinated High-Risk Subgroup in EPIC-SR

EPIC-SR was not powered to detect a treatment effect in this subgroup. Once PAXLOVID received an EUA in December 2021 for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of vaccination status, there was a lack of clinical equipoise to continue enrolling these subjects into a placebo-controlled trial, as vaccinated high-risk individuals could obtain PAXLOVID outside of a trial setting. Consequently, this analysis is limited to 631 vaccinated high-risk subjects who were enrolled prior to PAXLOVID receiving an EUA.

(2) The Seropositive Subgroup in EPIC-HR, to represent high-risk individuals who may have previously been infected with SARS-CoV-2 and as a surrogate for vaccinated adults.

- Baseline SARS-CoV-2 seropositivity may indicate some pre-existing SARS-CoV-2 immunity due to prior undiagnosed infection or may represent an early immune response to the current infection. Although immunity from prior infection is not identical to immunity from prior vaccination, the seropositive subgroup could be considered the EPIC-HR subgroup most representative of COVID-19 vaccinated adults. Analyses in this subgroup were considered supportive of the PAXLOVID EUA for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of COVID-19 vaccination status.

(3) The Seronegative Subgroup in EPIC-HR, for comparison.

<u>Reduction in the Endpoint of COVID-19 Related Hospitalization or Death From Any Cause Through Day 28</u>

The RRR for PAXLOVID for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was similar (>50%) in all three subgroups, noting the EPIC-SR vaccinated high-risk subgroup analysis was underpowered and did not reach statistical significance:

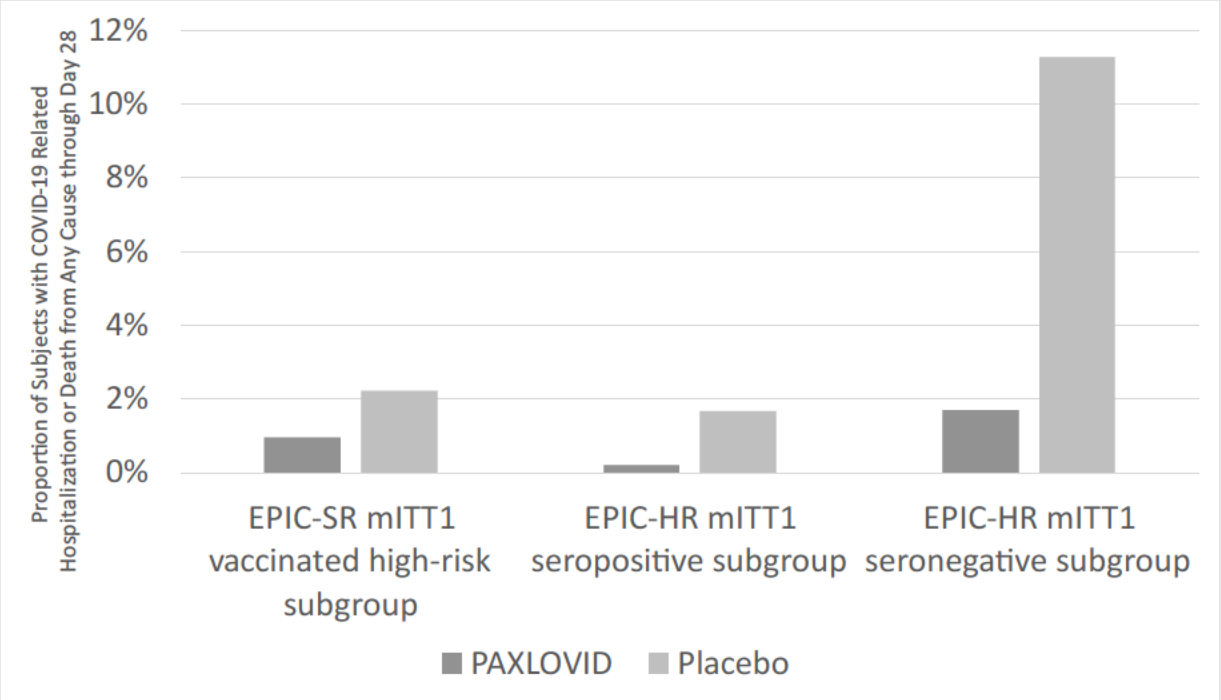
- In the EPIC-SR vaccinated high-risk subgroup, 3/317 (<1%) PAXLOVID recipients versus 7/314 (2%) placebo recipients met the composite endpoint, for a RRR of 58% (nominal p-value=0.2).

- In the EPIC-HR seropositive subgroup, 1/490 (<1%) PAXLOVID recipients versus 8/479 (2%) placebo recipients met the composite endpoint, for a RRR of 88% (nominal p-value=0.02).
- In the EPIC-HR seronegative subgroup, 8/475 (2%) PAXLOVID recipients versus 56/497 (11%) placebo recipients met the composite endpoint, for a RRR of 85% (nominal p-value<0.0001).

Source: Applicant's Table 84b.2.4.6.1.f from their December 5, 2022, submission and Applicant's Figure 841.2.1.24 from their November 23, 2022, response to an FDA information request. P-values were based on difference in estimated proportions using the Kaplan-Meier method.

Please see Figure 13. While the RRR with PAXLOVID versus placebo was similar in all three subgroups, the absolute risk reduction was lower in the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups. This is because pre-existing SARS-CoV-2 immunity either from prior infection or prior COVID-19 vaccination reduces the risk of severe COVID-19 outcomes. The absolute risk for COVID-19 related hospitalization or death from any cause through Day 28 in the placebo group was ~2% in the EPIC-HR seropositive and the EPIC-SR vaccinated high-risk subgroups versus 11% in the EPIC-HR seronegative subgroup. Notably, the impact of SARS-CoV-2 seropositivity in reducing the risk of severe outcomes is illustrated further by the following: in the vaccinated high-risk subgroup in EPIC-SR, 2/15 (13%) of the subjects who were baseline SARS-CoV-2 seronegative despite vaccination met the hospitalization/death endpoint versus 8/611 (1%) of the subjects who were baseline SARS-CoV-2 seropositive.

Figure 13. Proportion of High-Risk Subjects With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28



Sources: EPIC-SR Table 84b.2.4.6.1.f from the Applicant's December 5, 2022, submission, verified by the ADSL and ADHosp datasets, and EPIC-HR Figure 841.2.1.24 from the Applicant's November 23, 2022 submission.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat

Other Clinical Efficacy Endpoints

In the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups, benefit or trends toward benefit with PAXLOVID were observed for other clinical efficacy endpoints for which benefit was seen with PAXLOVID in the EPIC-HR seronegative subgroup as outlined below. However, as with the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 discussed above, outcomes were more favorable overall regardless of treatment in the EPIC-SR vaccinated high-risk and the EPIC-HR seropositive subgroups versus the seronegative subgroup in EPIC-HR.

Time to Sustained Alleviation of All Targeted Signs/Symptoms Through Day 28: median (95% CI) days for PAXLOVID versus placebo recipients, p-value

- EPIC-SR vaccinated high-risk subgroup: 12 (10, 14) versus 13 (11, 14), nominal p-value=0.9749
- EPIC-HR seropositive subgroup: 12 (11, 13) versus 14 (13, 15), nominal p-value=0.0095
- EPIC-HR seronegative subgroup: 13 (12, 15) versus 17 (16, 19), nominal p-value<0.0001

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADSO/ADSL datasets using log rank test.

Time to Sustained Resolution of All Targeted Signs/Symptoms Through Day 28: median (95% CI) days for PAXLOVID versus placebo recipients, p-value

- EPIC-SR vaccinated high-risk subgroup: 15 (13, 16) versus 15 (14, 17), nominal p-value=0.9523
- EPIC-HR seropositive subgroup: 15 (13, 16) versus 16 (15, 19), nominal p-value=0.0479
- EPIC-HR seronegative subgroup: 19 (17, 20) versus 23 (19, 25), nominal p-value=0.0026

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADSO/ADSL datasets using log rank test.

Note: The time to sustained symptom alleviation and time to sustained symptom resolution endpoints should be interpreted with caution given the large amount of missing data, potential data anomalies, symptom relapse after achieving the defined alleviation/resolution, and the lower symptom alleviation/resolution rates on Day 28 in the PAXLOVID group in the EPIC-SR vaccinated high-risk subgroup analyses (see Section 6.2.1.4 for more details).

All-Cause Mortality Through Week 24

- EPIC-SR vaccinated high-risk subgroup: 0/317 PAXLOVID recipients versus 1/314 (<1%) placebo recipients died (nominal p-value=0.498 by Fisher's exact test)
- EPIC-HR seropositive subgroup: 0/490 PAXLOVID recipients versus 3/479 (<1%) placebo recipients died (nominal p-value=0.1204 by Fisher's exact test)
- EPIC-HR seronegative subgroup: 0/475 PAXLOVID recipients versus 12/497 (2%) placebo recipients died (nominal p-value=0.0005 by Fisher's exact test)

Source: Applicant's Tables 84b.69b.5 and 84a.69a.5 from their December 5, 2022, response to an FDA information request.

COVID-19 Related Medical Visits Through Day 34

- EPIC-SR vaccinated high-risk subgroup: 7/317 (2%) PAXLOVID recipients versus 17/314 (5%) placebo recipients, nominal p-value=0.0579
- EPIC-HR seropositive subgroup: 8/490 (2%) PAXLOVID recipients versus 15/479 (3%) placebo recipients, nominal p-value=0.1864
- EPIC-HR seronegative subgroup: 14/475 (3%) PAXLOVID recipients versus 67/497 (14%) placebo recipients, nominal p-value<0.0001

Source: Reviewer's analyses on EPIC-HR and EPIC-SR ADHOSP/ADSL datasets using Pearson's Chi-squared test with continuity correction.

Nasopharyngeal Viral RNA Changes Over Time

In exploratory analyses, PAXLOVID treatment led to significantly greater reductions in NP SARS-CoV-2 viral RNA shedding levels compared to placebo from baseline to Day 5 in all three subgroups, although baseline viral RNA levels were numerically higher overall in the EPIC-HR seronegative subgroup. The Applicant conducted a statistical analysis of change from baseline to Day 5 in $\log_{10}$ transformed viral RNA levels (copies/mL) from NP samples. The analysis of covariance model included treatment, geographic region, symptom onset duration (≤3, >3 days), and baseline viral RNA level as covariates. Baseline SARS-CoV-2 serology status was also a covariate in the EPIC-SR vaccinated high-risk subgroup analysis. PAXLOVID conferred an additional mean reduction (SE) of -0.84 (0.14) $\log_{10}$ copies/mL in the EPIC-SR vaccinated high-risk subgroup ($p \leq 0.0001$), -0.47 (0.12) $\log_{10}$ copies/mL in the EPIC-HR seropositive subgroup ($p \leq 0.0001$), and -1.01 (0.11) $\log_{10}$ copies/mL in the EPIC-HR seronegative subgroup ($p \leq 0.0001$). Please see Table 27 below.

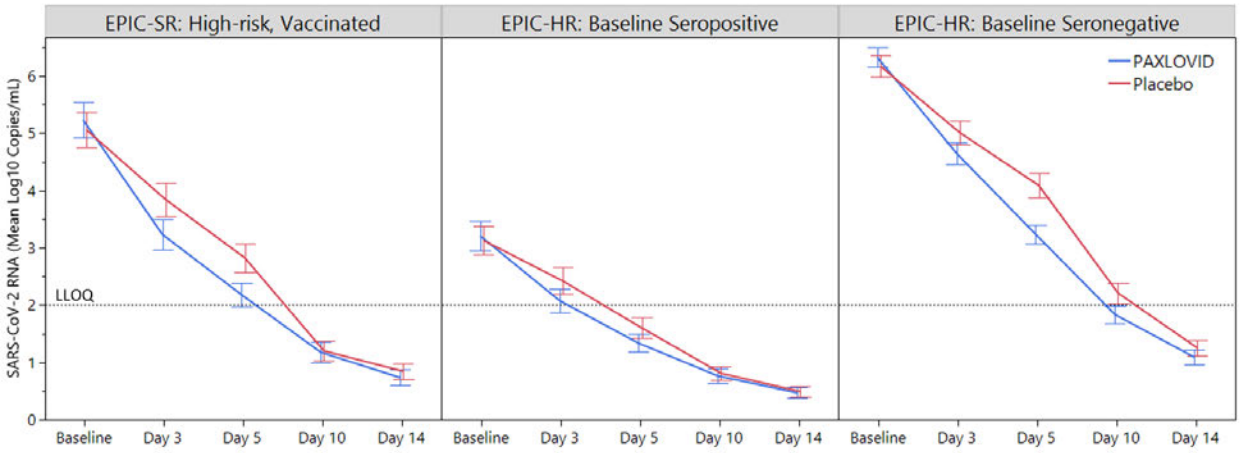
Table 27. Change From Baseline to Day 5 in SARS-CoV-2 RNA Levels in Nasopharyngeal Samples ($\log_{10}$ Transformed Copies/mL)

SARS-COV-2 RNA Measure	EPIC-SR Vaccinated HR PAXLOVID	EPIC-SR Vaccinated HR PBO	EPIC-HR Seropositive PAXLOVID	EPIC-HR Seropositive PBO	EPIC-HR Seronegative PAXLOVID	EPIC-HR Seronegative PBO
Baseline, n	256	257	320	330	436	444
Baseline mean (SD)	6.21 (1.86)	6.00 (1.87)	4.75 (2.23)	4.45 (2.22)	6.54 (1.59)	6.50 (1.60)
Day 5, n	246	238	280	296	396	387
Day 5 mean (SD)	2.58 (1.76)	3.32 (2.02)	1.88 (1.70)	2.22 (1.98)	3.32 (1.65)	4.31 (2.06)
Change* from BL, n	245	236	280	296	396	387
Change from BL mean (SE)*	-3.35 (0.23)	-2.51 (0.23)	-2.72 (0.09)	-2.26 (0.09)	-3.31 (0.17)	-2.30 (0.17)

Source: Information taken from the Applicant's Tables 84b.2.2.16.f and 84a.2.2.12 submitted on December 5, 2022.
* Least squares mean difference
Abbreviations: BL, baseline; HR, high risk; log, logarithm; n, number of subjects in specified population or group; PBO, placebo; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error; SD, standard deviation

FDA independent analyses, shown in Figure 14 below, were generally consistent with the Applicant's findings.

Figure 14. SARS-CoV-2 RNA Levels Over Time



Source: FDA analysis of EPIC-HR and EPIC-SR ADSL and ADMC datasets
Abbreviations: log, logarithm; LLOQ, lower limit of quantitation; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Real-*World Evidence*

Since PAXLOVID was authorized for emergency use in December 2021, FDA has monitored the published literature on real-world evidence (RWE) studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations. Most of the data sources used in these published RWE studies had insufficient longitudinal data and/or inappropriate study design to account for potential bias.

Among the identified studies, five are based on appropriate source data and implemented design features that can account for the potential bias introduced by "index time" selection. These five retrospective cohort studies estimated the effectiveness of PAXLOVID by COVID-19 vaccination status, or in a vaccinated population only. In general, these studies had similar findings to the clinical trials (i.e., PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status). However, while the source data and certain design elements of these cohort studies were appropriate, there were insufficient details on the data source, methods, or analytical approach for a complete review to determine the quality of the results of the studies. Please see Section 16.5 for more details.

Safety Data

Safety findings did not differ in the clinical trials by vaccination status or by baseline serology. Based on EPIC-HR safety data combined with the interim data from EPIC-SR (December 19, 2021, data cutoff), incidence of treatment-emergent adverse events (TEAEs) was 25% and 27% in the vaccinated subgroup, versus 22% and 24% in the unvaccinated subgroup, for PAXLOVID and placebo recipients, respectively. Likewise, incidence of TEAEs among PAXLOVID recipients was similar in the seropositive versus seronegative subgroups (24% versus 22%). In all subgroups, the most common TEAE among PAXLOVID recipients was dysgeusia followed by diarrhea. Please see Section 17.3 for more details.

Conclusion

The EPIC-HR and EPIC-SR clinical trial results support the efficacy of PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. While pre-existing SARS-CoV-2 immunity, either from vaccination or prior infection, is among the factors that impact the risk of progression to severe COVID-19, the RRR with PAXLOVID versus placebo for COVID-19 related hospitalization or death from any cause appears to be similar in high-risk subjects regardless of prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus. Similar patterns were seen with other efficacy endpoints. In addition, PAXLOVID led to significant additional reductions in SARS-CoV-2 viral RNA shedding levels in NP swabs through Day 5 versus placebo in high-risk subjects regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. In terms of risk, prior vaccination and baseline seropositivity had no discernible impact on the safety of PAXLOVID.

Healthcare providers should consider the benefit-risk for individual patients, including those who have received prior COVID-19 vaccination or been previously infected with SARS-CoV-2. Factors that impact the risk of progression to severe COVID-19, such as vaccination status, age, and cardiovascular disease, should be considered when making individual treatment decisions along with factors that may impact the risk of PAXLOVID use, such as drug interactions with concomitant medications that may result in significant adverse reactions.

6.3.3. Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

Issue

Is PAXLOVID likely to retain efficacy against the SARS-CoV-2 Omicron variant?

Background

The pivotal trial EPIC-HR, which showed efficacy of PAXLOVID based on the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28, enrolled subjects in the timeframe of July to November 2021. During this period, the SARS-CoV-2 Delta variant was predominant in the United States and throughout most of the world, and this preceded the emergence and global spread of the SARS-CoV-2 Omicron variant and sub-variants. As expected, the study population in EPIC-HR was primarily (~99%) infected with the SARS-CoV-2 Delta variant, and the Omicron variant was not observed.

Soon after the completion of EPIC-HR, the Omicron variant (and in particular the Omicron sub-variant BA.1) quickly became predominant and replaced the SARS-CoV-2 Delta variant in the United States and worldwide. Currently, Omicron sub-variants are responsible for essentially all SARS-CoV-2 infections in the United States, with the Omicron sub-variants XBB.1.5 and XBB.1.9.1 most commonly detected (CDC 2023c).

While the second half of the EPIC-SR trial was conducted from March to June 2022, in a study population infected with the SARS-CoV-2 Omicron variant (based on 89% of subjects with available variant data, 100% had an Omicron variant, mostly BA.2-related), data from this trial were insufficient to directly determine the clinical efficacy of PAXLOVID in patients infected

with the Omicron variant and at high risk for progression to severe COVID-19. Enrollment during this period was restricted to subjects at low risk for severe disease given high-risk subjects could obtain PAXLOVID under EUA, and no subjects during this period reached the secondary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28.

Assessment

Despite the lack of clinical trial data to directly determine the clinical efficacy of PAXLOVID in high-risk adults infected with the SARS-CoV-2 Omicron variant, nonclinical and clinical data demonstrate that PAXLOVID retains antiviral activity against the SARS-CoV-2 Omicron variant. Using biochemical assays, the activity of nirmatrelvir was determined against recombinant SARS-CoV-2 M^{pro} enzymes containing naturally occurring amino acid polymorphisms, including P132H, a common polymorphism in the Omicron variant and subvariants. Nirmatrelvir retained activity (K_i fold-change <3) against SARS-CoV-2 M^{pro} enzymes with naturally occurring polymorphisms (e.g., G15S, T21I, L75F, K88R, L89F, K90R, P108S, P132H, T169S, and A260V). In cell culture, nirmatrelvir retained activity (EC_{50} value fold-change <3) against different SARS-CoV-2 variants, including Alpha, Gamma, Delta, Lambda, Mu, and Omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, and XBB.1.5 (see Section 20). Literature reports have also indicated that nirmatrelvir retains activity against several SARS-CoV-2 variants in cell culture, including Omicron subvariants BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and XBB (Abdelnabi et al. 2022; Bojkova et al. 2022a; Bojkova et al. 2022b; Li et al. 2022; Ohashi et al. 2022; Saito et al. 2022; Takashita et al. 2022a; Takashita et al. 2022b; Takashita et al. 2022c; Vangeel et al. 2022; Imai et al. 2023). Nirmatrelvir was also demonstrated to have antiviral activity against other human coronaviruses in cell culture, including SARS-CoV-1, MERS-CoV, and HCoV-229E.

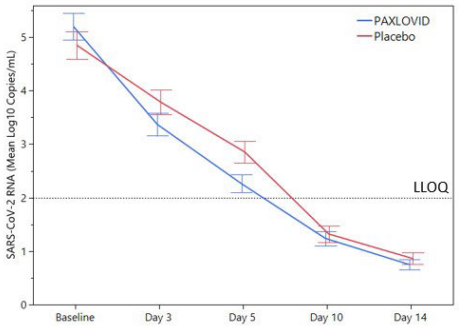
In addition, bioinformatic analyses of M^{pro} and M^{pro} cleavage site amino acid sequence conservation were provided based on the GISAID EpiCoV sequence database (n=12.7 million sequences, accessed November 30, 2022). Note that these analyses are affected by global disparities in SARS-CoV-2 genomic surveillance. Only 10 M^{pro} polymorphisms and 5 M^{pro} cleavage site polymorphisms were found to have a cumulative frequency ≥0.1%. None of the 10 M^{pro} polymorphisms significantly affected nirmatrelvir activity in biochemical assays (K_i fold-change <3). The effects of the M^{pro} cleavage site polymorphisms have not been determined, but M^{pro} cleavage site substitutions outside of M^{pro} have not been associated with nirmatrelvir resistance in cell culture studies. Overall, these analyses demonstrate that SARS-CoV-2 M^{pro} and M^{pro} cleavage sites are highly conserved and that nirmatrelvir is likely to retain activity against circulating and emerging variants of SARS-CoV-2. More recent analyses of sequences through January 31, 2023 are consistent with these findings.

Lastly, analysis of viral RNA shedding data from EPIC-SR subjects who enrolled in the 2022/Omicron enrollment period (March to June 2022) found that PAXLOVID retained antiviral activity against the SARS-CoV-2 Omicron variant in treated subjects (Figure 15). Compared to placebo, PAXLOVID treatment was associated with a more rapid decline in viral RNA levels in NP samples in both the 2021/pre-Omicron enrollment period and in the 2022/Omicron enrollment period. In the 2021/pre-Omicron period, ~98% of subjects with available viral sequence data were infected with the SARS-CoV-2 Delta variant, similar to EPIC-HR, while in

the 2022/Omicron period, all subjects with available data were infected with the SARS-CoV-2 Omicron variant (mostly BA.2-related subvariants).

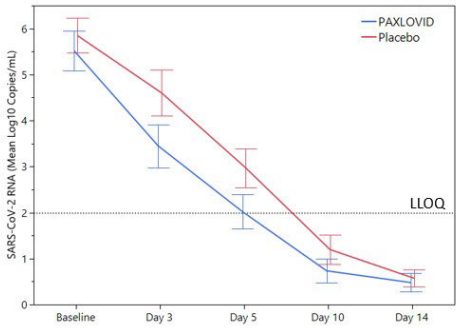
Figure 15. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples (mITT1 Analysis Set), According to Enrollment Year

2021: Pre-Omicron Period (n=539 PAXLOVID, n=528 Placebo)



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.93	-2.01
% (n/N) <LLOQ	49.3% (251/509)	40.4% (199/492)

2022: Omicron Period (n=114 PAXLOVID, n=106 Placebo)



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.52	-2.85
% (n/N) <LLOQ	56.6% (60/106)	36.5% (38/104)

Source: FDA analysis of ADMC and ADSL datasets.
Note: Charts show mean values and 95% confidence intervals.
Abbreviations: EOT, end-of-treatment; BL, baseline; cp/mL, copies per milliliter; LLOQ, lower limit of quantification; N number of subjects with available data; n in table, number of subjects with viral RNA <LLOQ; n in graph title, number of subjects in treatment group

Conclusion

Based on nonclinical and clinical virology data, PAXLOVID was found to retain antiviral activity against the SARS-CoV-2 Omicron variant and major subvariants, and PAXLOVID is considered likely to retain activity against circulating and emerging variants given the high conservation (based on amino acid identity) of M^{pro} and M^{pro} cleavage site amino acid sequences. Although clinical trial data to assess clinical efficacy against the SARS-CoV-2 Omicron variant are limited, based on the available virology data it is reasonable to conclude that PAXLOVID is likely to retain clinical efficacy in adults with COVID-19 caused by the SARS-CoV-2 Omicron variant, and who are at high risk of progression to severe disease.

Through our monitoring of the RWE publications, we identified five retrospective cohort RWE studies that used appropriate source data and with acceptable design to estimate the effectiveness of PAXLOVID in reducing hospitalization and death from COVID-19 during periods when the SARS-CoV-2 Omicron variant was predominant. While these reports also indicate that PAXLOVID is likely to retain clinical efficacy against COVID-19 caused by the SARS-CoV-2 Omicron variant, these published studies do not provide sufficient information for a complete review to determine their quality (see Section 16.5 for additional details).

6.3.4. Efficacy in High-Risk Patients With Mild Disease

Issue

Is the benefit-risk assessment favorable for PAXLOVID for the treatment of both mild COVID-19 and moderate COVID-19 in high-risk individuals?

Background

EPIC-HR, the pivotal trial which demonstrated an 86% relative risk reduction for PAXLOVID in the composite endpoint of COVID-19 related hospitalization or death from any cause through Day 28, enrolled adults at high risk for progression to severe disease with either mild or moderate COVID-19 at study entry. Per the protocol, enrolled subjects had to have confirmed SARS-CoV-2 infection, at least one of the prespecified signs/symptoms attributable to COVID-19 on the day of randomization, oxygen saturation ≥92%, and no current need or anticipated need within 48 hours for hospitalization. While these criteria ensured that enrollment was limited to patients with mild or moderate COVID-19, per the protocol subjects were not further classified as to whether their COVID-19 was mild versus moderate.

Mild versus moderate COVID-19 is defined as follows:

- Per National Institutes of Health (NIH) COVID-19 Treatment Guidelines (NIH 2022a):
  - Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
  - Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO2) ≥94% on room air at sea level.
- Per the FDA Guidance for Industry, COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (May 2020):
  - Mild COVID-19:
    - Positive testing by standard RT-PCR assay or equivalent test
    - Symptoms of mild illness with COVID-19 that include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
    - No clinical signs indicative of moderate, severe, or critical severity
  - Moderate COVID-19:
    - Positive testing by standard RT-PCR assay or equivalent test
    - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
    - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO_2) >93% on room air at sea level, heart rate ≥ 90 beats per minute
    - No clinical signs indicative of severe or critical illness severity

Since the EUA of PAXLOVID in December 2021, there have been articles questioning whether PAXLOVID should be taken by patients who are only mildly ill (Morgan M 2022; Sheikh 2023). In order to further inform on the benefit of PAXLOVID in patients with mild illness, a post hoc analysis was performed to determine the benefit of PAXLOVID in preventing COVID-19 related hospitalization or death from any cause through Day 28 by subgroup of baseline COVID-19 disease severity.

Assessment

Methods

The mITT1 EPIC-HR analysis population (N=977 PAXLOVID recipients and N=989 placebo recipients) was used for this post hoc analysis. "Baseline" was defined as any analysis visit designated as "baseline" in the datasets, which could include both screening and Day 1 study visits, and the maximum analysis value was used in situations where there was more than one entry for a baseline analysis visit.

Two different definitions of moderate illness (which included symptom data and vital signs but not imaging results) were used. The first definition was based on the description of moderate COVID-19 in NIH COVID-19 Treatment Guidelines and in the FDA Guidance. The second definition was based on the maximum severity of overall symptoms, because illness severity is often defined in the general population based on the severity of any symptom rather than the presence of lower respiratory disease. In both cases, mild illness was defined as the absence of any criteria necessary for moderate illness by that specific definition. The definitions for moderate illness were as follows:

- **Moderate COVID-19**: at baseline, any shortness of breath, heart rate ≥ 90 beats per minute, or respiratory rate ≥ 20 breaths per minute.
- **Moderate COVID-19 symptoms**: at baseline, any symptom with greater than mild severity among all the reported COVID-19 symptoms. COVID-19 symptoms included chills or shivering, cough, diarrhea, feeling hot or feverish, headache, low energy or tiredness, muscle or body aches, nausea, loss of sense of smell, loss of sense of taste, shortness of breath or difficulty breathing, sore throat, stuffy or runny nose, and vomiting.
  - Symptoms were not reported at baseline for 57 PAXLOVID recipients and 34 placebo recipients, these subjects were not included in this particular analysis.

Results

While a higher proportion of subjects with moderate versus mild illness met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28, PAXLOVID significantly reduced the rate of primary endpoint events in both the moderate and mild illness subgroups. Please see Table 28 below.

Table 28. Proportion of Subjects Who Met the Primary Endpoint of COVID-19 Related Hospitalization or Death From Any Cause Through Day 28 by Baseline Illness Severity (mITT1 Analysis Population)

Primary Endpoint in Subjects With Mild COVID-19 at BL[a]	**PAXLOVID N=355**	**Placebo N=324**
Subjects with event, n (%)	0	16 (4.9%)
Difference in proportion	4.9%	
Nominal p-value	<0.0001	
Primary Endpoint in Subjects With Moderate COVID-19 at BL[b]	**PAXLOVID N=622**	**Placebo N=665**
Subjects with event, n (%)	9 (1.4%)	48 (7.2%)
Difference in proportion	5.8%	
Nominal p-value	<0.0001	

Primary Endpoint in Subjects With Mild COVID-19 Symptoms at BL[c]	PAXLOVID N=173	Placebo N=184
Subjects with event, n (%)	0	6 (3.2%)
Difference in proportion	3.2%	
Nominal p-value	0.0304	
Primary Endpoint in Subjects With Moderate COVID-19 Symptoms at BL[d]	**PAXLOVID N=747**	**Placebo N=771**
Subjects with event, n (%)	8 (1.1%)	57 (7.4%)
Difference in proportion	6.3%	
Nominal p-value	<0.0001	

Source: EPIC-HR ADSL, ADSO, and ADVS datasets.
Note: P-values are based on Fisher's exact test.
[a.] Mild COVID-19 at Baseline": no shortness of breath, no heart rate ≥90 beats per minute, and no respiratory rate ≥20 breaths per minute.
[b.] Moderate COVID-19 at Baseline: either shortness of breath, heart rate ≥ 90 beats per minute, and/or respiratory rate ≥ 20 breaths per minute).
[c.] Mild COVID-19 Symptoms at Baseline: no symptom with greater than mild severity at baseline among all the reported COVID-19 symptoms).
[d.] Moderate COVID-19 Symptoms at Baseline: any symptom with greater than mild severity at baseline among all the reported COVID-19 symptoms).
Abbreviations: BL, baseline; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with specified characteristic

Conclusion

Post hoc analyses of EPIC-HR data support the efficacy of PAXLOVID for the treatment of mild to moderate COVID-19 in high-risk adults regardless of whether the baseline illness severity is mild or moderate.

6.3.5. Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

Issue

What is the optimal duration of PAXLOVID treatment for mild to moderate COVID-19 in patients who are moderately or severely immunocompromised?

Background

The two Phase 2/3 COVID-19 treatment trials supporting the NDA, the pivotal trial, EPIC-HR, and the supportive trial, EPIC-SR, evaluated 5 days of treatment with PAXLOVID versus placebo. EPIC-HR demonstrated an 86% relative risk reduction with 5 days of PAXLOVID treatment for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28 among adults with laboratory-confirmed, symptomatic SARS-CoV-2 infection who had at least one risk factor that put them at high risk for progression to severe disease, who had not received any dose of a COVID-19 vaccine, and who began treatment within 5 days of symptom onset. However, only 13/2246 subjects (<1%) in the full analysis set in EPIC-HR were classified as having immunosuppression.

Patients with moderate to severe immunocompromise might benefit from a longer treatment course of PAXLOVID based on the clinical course of COVID-19 in this population. While most people with mild-to-moderate COVID-19 are expected to clear their infection within 10 days of symptom onset, individuals with moderate to severe immunocompromise can remain infectious beyond 20 days (CDC 2022a). Persistent SARS-CoV-2 infection, defined as SARS-CoV-2 RNA

detection ≥30 days after initial positivity, was reported in 14% (51/368) of patients with hematologic malignancies who were diagnosed with COVID-19 from March 10, 2020, to February 28, 2021, at one center and were alive 30 days after their COVID-19 diagnosis; receipt of anti-CD20 therapy within the prior year, cellular therapy including hematopoietic stem cell transplantation within 1 year, and chronic lymphopenia were associated with persistent SARS-CoV-2 infection on multivariate analysis in this study (Lee et al. 2022). Risks of persistent SARS-CoV-2 infection include morbidity and mortality from COVID-19, interruption in treatment for cancer and other medical conditions, SARS-CoV-2 transmission to contacts, and the potential evolution of the SARS-CoV-2 virus.

Assessment

Clinical Trial Data

Currently available clinical trial data are limited on use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in patients with moderate to severe immunocompromise. As noted above, <1% (13/2246) of enrolled subjects in EPIC-HR were classified as having immunosuppression, six of whom were randomized to PAXLOVID versus seven to placebo. Of these 13 subjects, five were on immunosuppressive medications for rheumatoid arthritis, two were on immunosuppressive medications for systemic lupus erythematosus (SLE), three were on immunosuppressive medications for other conditions (ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis), one had SLE, one had acute myeloid leukemia (AML) and was taking immunosuppressive medications, and one had breast cancer and was taking chemotherapy and other immunosuppressive medications. None of these 13 subjects experienced the primary outcome of COVID-19 related hospitalization or death from any cause through Day 28, although one of the subjects who received placebo died on Day 97 due to sepsis with underlying relapsed AML. SARS-CoV-2 viral RNA levels through Day 14 from these 13 immunosuppressed subjects were within the range observed in the overall population, with no evidence of increased levels after treatment ended on Day 5 among the PAXLOVID recipients.

Emergency IND Data

Some (>20) severely immunosuppressed patients with prolonged persistent SARS-CoV-2 infection (up to 6 months) have received longer courses of PAXLOVID of 10 to 28 days duration under emergency INDs. Of the 15 patients with outcome data, 2 died: 1 was hospitalized in the intensive care unit at baseline and died on Day 2 of PAXLOVID treatment, 1 had decreasing SARS-CoV-2 RNA levels at the time of death and other complications such as cavitary pulmonary aspergillosis. The remaining 13 patients with outcome data improved in terms of symptoms, SARS-CoV-2 viral testing, or both. Clinical improvement or complete resolution of symptoms was reported in 11 patients; viral clearance was also reported for 5 of these patients (no SARS-CoV-2 viral level information after PAXLOVID initiation was reported for the other 6 patients). For the remaining 2 patients, viral clearance was reported; persistent symptoms were reported for 1 of these patients, and no information on symptoms was provided for the other patient. The clinical courses of 2 of the 15 patients have been published as case reports (Ford et al. 2022; Trottier et al. 2022). The small number of patients, combined with their variable use of other concurrent antiviral medications like remdesivir or anti-SARS-CoV-2 therapeutic mAb therapy and their variable health status at treatment initiation, as well as the lack of a control group, precludes drawing any conclusions from these cases.

Quantitative Systems Pharmacology Modeling

Quantitative systems pharmacology (QSP) modeling suggests a potential benefit for longer duration PAXLOVID treatment (e.g., 10 days) in viral RNA reduction in immunocompromised patients (see Section 14.5). The Applicant used QSP models and virtual populations to predict the optimal duration of treatment in both the overall PAXLOVID-eligible population and the immunocompromised population. This QSP modeling attempted to account for the effects of the immune system on SARS-CoV-2 replication in infected patients and was developed using longitudinal data from observational studies in SARS-CoV-2 infected subjects who measured immune markers in the blood (e.g., serum cytokine levels) and SARS-CoV-2 RNA levels in NP samples. Clinical trial data from studies of SARS-CoV-2 antiviral products (i.e., bamlanivimab/etesevimab, casirivimab/imdevimab, and molnupiravir) also informed the QSP model. The virtual immunocompromised patients were generated by two approaches: a mechanistic approach that attenuates Type I IFN and $CD8^+$ T cell-mediated killing of infected cells which induces a prolonged viral shedding profile, and a phenotypic approach that selects PAXLOVID-eligible virtual patients who exhibit a long viral RNA shedding. QSP modeling of 5, 10, or 15 days of PAXLOVID treatment indicated the following: while extending treatment beyond 5 days in the overall PAXLOVID-eligible population under the EUA was not predicted to offer additional benefit for SARS-CoV-2 viral RNA suppression, this strategy could aid in reducing viral RNA to undetectable levels in the immunocompromised population, whose viral RNA shedding (in $\log_{10}$ scale) was predicted to be approximately twice that of the overall PAXLOVID-eligible population by Day 5 of treatment. In the immunocompromised population model, 10 days of PAXLOVID treatment was predicted to be sufficient for optimal viral RNA suppression (although 5 days of PAXLOVID treatment was still predicted to decrease viral RNA more quickly than placebo). The QSP modeling data support investigating longer durations of PAXLOVID treatment in the immunocompromised population in a clinical trial setting, where the impact of longer treatment duration on DDI management can also be evaluated in this population.

Conclusion

More data, including clinical trial data, are needed to determine if a longer duration of PAXLOVID dosing may be optimal for treatment of mild-to-moderate COVID-19 in patients who are moderately or severely immunocompromised. The PAXLOVID EUA was modified on August 05, 2022, to add the following condition of authorization: “Pfizer will conduct a randomized controlled trial to evaluate different durations of PAXLOVID treatment in immunocompromised patients with mild-to-moderate COVID-19. Pfizer will provide topline results by September 30, 2023.” This trial, EPIC-IC (or C4671034, NCT05438602), is a double-blind study in which immunocompromised subjects with mild to moderate COVID-19 are randomized to 5, 10, or 15 days of PAXLOVID treatment; EPIC-IC began enrollment in September 2022 (ClinicalTrials.gov: NCT05438602 2023). The ongoing trial is recommended as postmarketing commitment (PMC) for inclusion in the Approval Letter to inform if there is a need for longer PAXLOVID treatment duration (e.g., 10 days or 15 days versus 5 days) in patients who are immunocompromised.

6.3.6. Impact of PAXLOVID on COVID-19 Rebound

Issue

What is the rate and clinical significance of virologic and symptomatic COVID-19 rebound, and is it affected by PAXLOVID treatment?

Background

Following the EUA with resulting widespread use of PAXLOVID for the treatment of outpatients with COVID-19, several publications, case reports, and stories in the press described patients with COVID-19 who experienced symptomatic recovery during PAXLOVID treatment, but experienced "relapses" in COVID-19 symptoms after stopping the 5-day course of treatment, which in some cases coincided with rebounds in qualitative or quantitative viral RNA, antigen, or virus detection in upper respiratory tract samples (Antonelli et al. 2022; Boucau et al. 2022; Carlin et al. 2022; Charness et al. 2022; Epling et al. 2022; Ranganath et al. 2022). Likewise, through August 29, 2022, 2143 cases were reported through the FDA Adverse Events Reporting System (FAERS) that described a rebound of COVID-19 symptoms after PAXLOVID use, which occurred on average 6 days after treatment completion (DARRTS ID: 5077785 2022).[2] These cases have occurred in patients with varying demographics including immunocompetent, vaccinated individuals. Symptoms during COVID-19 rebound have generally been reported to be mild. These reports have raised speculation that PAXLOVID treatment may incompletely suppress virus replication or delay the development of a functional host immune response that is ultimately responsible for clearing the infection, resulting in a rebound in viral replication and COVID-19 symptoms following the 5-day treatment course (Rubin 2022; Focosi et al. 2023). Some researchers have also speculated that symptomatic or virologic rebound may be associated with the SARS-CoV-2 Omicron variant or subvariants (Rubin 2022). Others have reported widely varying rates of symptomatic or virologic rebound following treatment with PAXLOVID or molnupiravir, or even in the absence of any antiviral treatment (Deo et al. 2022; Pandit et al. 2022; Wang et al. 2022; Wong et al. 2022).

Despite the publications and widespread reporting in the press of COVID-19 rebound following PAXLOVID treatment, it has been challenging to determine the direct contribution of PAXLOVID treatment to virologic or symptomatic rebound from published reports. Other than analyses from the Applicant based on data from the EPIC-HR trial, published reports and analyses of COVID-19 rebound are based on case reports and non-randomized, observational cohort studies (Anderson et al. 2022).

The systematically collected virology and symptom data from the randomized, placebo-controlled EPIC-HR and EPIC-SR trials allowed for in-depth analyses to investigate the rates of virologic and symptomatic rebound, to assess whether PAXLOVID treatment (compared to placebo) is specifically associated with this phenomenon, and to compare rebound rates in the 2021 (pre-Omicron) and 2022 (Omicron) periods.

[2] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

Assessment

Analyses of SARS-CoV-2 RNA Rebound in EPIC-HR and EPIC-SR

The likelihood of detecting viral RNA rebound is impacted substantially by the analysis definition, frequency of testing, and number of test results considered. FDA analyses used the following analysis parameters to detect and characterize post-treatment viral RNA rebound in NP samples from Day 5 (end-of-treatment) through either Day 10 or Day 14, which were the post-treatment visits with available virology data:

- **Day 10 (lower limit of quantification [LLOQ]/0.5 Combined)**: Day 5 RNA <LLOQ AND at Day 10 RNA ≥LLOQ, OR, Day 5 RNA ≥LLOQ AND Day 10 RNA ≥0.5 $\log_{10}$ copies/mL increase from Day 5.
- **Day 14 (LLOQ/0.5 Combined)**: Day 5 RNA <LLOQ AND at Day 14 RNA ≥LLOQ, OR, Day 5 RNA ≥LLOQ AND Day 14 RNA ≥0.5 $\log_{10}$ copies/mL increase from Day 5.
- **Day 10/14 (LLOQ/0.5 Combined)**: Met either definition of Day 10 (LLOQ/0.5 Combined) OR Day 14 (LLOQ/0.5 Combined).

Additional subgroup analyses were conducted among subjects with evidence of a virologic response through Day 5/end-of-treatment, defined as:

- **Day 5/EOT Virologic Responders**: Day 5 RNA <LLOQ, OR, ≥1 $\log_{10}$ copy/mL decline from BL to Day 5.
- **Day 5/EOT <LLOQ**: Day 5 RNA <LLOQ (i.e., subgroup of Day 5/EOT Virologic Responders).

The Day 10/14 definition was considered the primary definition of viral RNA rebound given it identified subjects with any evidence of viral RNA rebound from Day 5 to either Day 10 or Day 14. These analysis parameters were intended to provide a sensitive means to detect occurrences of post-treatment increases in viral RNA shedding levels, regardless of magnitude. The clinical relevance of any specific quantitative magnitude of viral RNA rebound is unknown. Viral RNA levels over time in individual subjects were also characterized to assess for different patterns between PAXLOVID- and placebo-treated subjects, for example whether the magnitude of post-treatment viral RNA increases clearly differ between PAXLOVID- and placebo-treated subjects. These analyses were conducted for the mITT2 population for EPIC-HR, and the mITT1 population for EPIC-SR, both of which include all subjects randomly assigned to study intervention who took at least 1 dose of study intervention.

Rates of post-treatment viral RNA rebound in EPIC-HR are summarized in Table 29. Based on the Day 10/14 (LLOQ/0.5 Combined) definition, post-treatment viral RNA rebound was observed in 8.3% of PAXLOVID recipients and 5.7% of placebo recipients (p=0.04, Fisher's Exact Test, not adjusted for multiplicity). In both treatment groups, higher rates of viral RNA rebound relative to Day 5/EOT were observed at Day 10 compared to Day 14, indicating most observations of rebound occurred by Day 10. Viral RNA levels for individual subjects who met the definitions of viral RNA rebound showed substantial heterogeneity in the viral RNA patterns, with no clear or consistent differences between PAXLOVID and placebo recipients in the RNA rebound patterns or magnitude of rebound.

While the Day 10/14 (LLOQ/0.5 Combined) definition showed a modest yet nominally significant higher rate of rebound overall in PAXLOVID recipients compared to placebo recipients, post-treatment (i.e., post-Day 5) viral RNA rebound was clearly not restricted to PAXLOVID recipients. Furthermore, calculated rates of viral RNA rebound could be biased by the greater impact of PAXLOVID on early viral RNA declines through Day 5. This definition would not capture subjects with viral RNA levels that declined slowly or remained relatively high through the treatment period (i.e., did not yet achieve a nadir level by Day 5). Post-Day 5 viral RNA rebound occurred almost exclusively among subjects with a virologic response through Day 5; 94% (119/126) of subjects with Day 10/14 viral RNA rebound had evidence of a virologic response through Day 5 (Day 5/EOT Virologic Responders), defined as Day 5 <LLOQ, or a ≥1 $\log_{10}$ copies/mL decline from baseline to Day 5.

Therefore, to compare post-treatment viral RNA rebound rates more directly between subjects with comparable on-treatment virologic responses, the Day 10/14 (LLOQ/0.5 Combined) analysis was restricted to PAXLOVID and placebo recipients who were considered Day 5/EOT Virologic Responders. In this subgroup of subjects, or in the smaller subset of subjects with viral RNA <LLOQ at Day 5, rates of viral RNA rebound after Day 5 remained modestly higher in PAXLOVID recipients, but the differences were no longer statistically significant (Table 29).

Table 29. EPIC-HR: Rates of Post-Treatment Viral RNA Rebound

Viral RNA Rebound Analysis	PAXLOVID Total N=1035	Placebo Total N=1048	p-Value[a]
Day 10 (LLOQ/0.5 combined)	6.6% (57/865)	4.7% (40/856)	0.09
Day 14 (LLOQ/0.5 combined)	2.6% (23/884)	1.9% (17/893)	0.34
Day 10/14 (LLOQ/0.5 combined)	8.3% (77/925)	5.7% (53/922)	0.04
Day 5/EOT Virologic responders: Day 10/14 (LLOQ/0.5 combined)	8.1% (69/849)	6.5% (50/772)	0.22
Day 5 <LLOQ: Day 10/14 (LLOQ/0.5 combined)	8.2% (36/440)	5.1% (21/410)	0.10

Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
[a.] Fisher's exact test, two-sided.
Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification; N, number of subjects in treatment group; RNA, r bonucleic acid

Regardless of any numeric differences in rates of post-treatment viral RNA rebound, PAXLOVID treatment ultimately did not result in delayed declines in viral RNA to unquantifiable levels. At all analysis visits, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ (Table 30). Based on these results, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely for a PAXLOVID-treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 30. EPIC-HR: Proportions of PAXLOVID or Placebo Subjects With Viral RNA <LLOQ at Each Analysis Visit

Day	PAXLOVID	Placebo
Day 3	35.1% (340/970)	32.8% (321/980)
Day 5/EOT	47.8% (447/936)	44.1% (415/942)
Day 10	76.1% (702/922)	68.9% (622/903)
Day 14	88.6% (835/942)	86.0% (815/948)

Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification; RNA, ribonucleic acid

Post-treatment viral RNA rebound in EPIC-HR was not associated with the primary clinical outcome of COVID-19 related hospitalization or death from any cause through Day 28. Among the 130 subjects who experienced Day 10/14 viral RNA rebound, only 4 subjects (3%) reached the hospitalization or death endpoint (0 deaths), including 1 PAXLOVID recipient and 3 placebo recipients. The hospitalization in the PAXLOVID recipient (Subject (b) (6)) occurred early during treatment and the subject was discharged from the hospital prior to the post-treatment viral RNA rebound.

Post-treatment viral RNA rebound in EPIC-HR was not associated with baseline immunosuppression risk, although this was a small subgroup of subjects in the trial (n=6 PAXLOVID, n=7 placebo). Only one of these subjects experienced post-treatment viral RNA rebound, and the subject received placebo.

Post-treatment viral RNA rebound in EPIC-HR generally was not associated with the emergence of potential nirmatrelvir drug resistance, although there were 2 subjects (3% of the 59 PAXLOVID treated subjects with viral RNA rebound and available viral sequence data) who had a treatment-emergent amino acid substitution detected in M^{pro} that is potentially associated with nirmatrelvir resistance, including E166V in one subject, and T304I in the second subject.

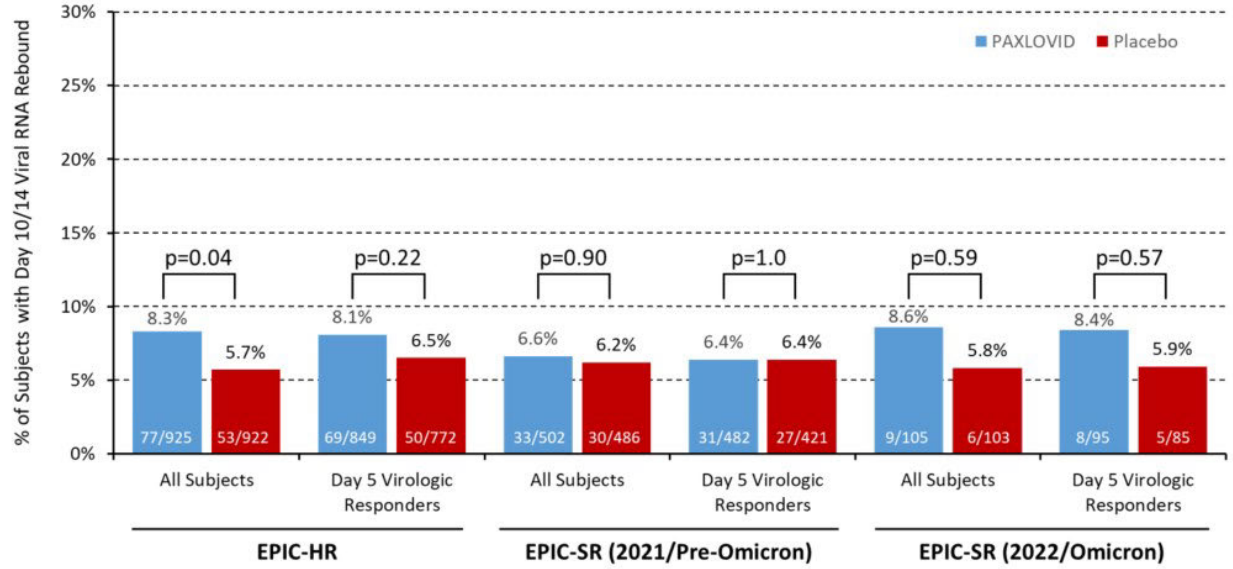
The Applicant also conducted analyses assessing for cell culture infectious virus in a subset of NP samples from subjects in EPIC-HR using two types of infectivity assays: a viral recovery assay and a viral titration immunoassay (i.e., median tissue culture infectious dose [$TCID_{50}$] assay). Considering either the viral recovery assay or the viral titration assay, among those who experienced Applicant-defined post-treatment viral RNA rebound, qualitatively positive test results for virus infectivity for Day 10 or Day 14 samples were observed in a small number of subjects, including subjects treated with PAXLOVID or placebo: 29% (18/62) and 39% (15/38) of PAXLOVID and placebo recipients, respectively.

In EPIC-SR, comparable rates of post-treatment viral RNA rebound were observed between PAXLOVID and placebo recipients, with no analyses indicating statistically significant differences in rebound rates between the two groups. Furthermore, although the numbers of subjects who had Omicron variants detected or who enrolled in the Omicron period were relatively small, there were no significant differences in rebound rates between PAXLOVID and placebo recipients regardless of whether they were determined to be infected with a SARS-CoV-2 Delta or Omicron variant, or more broadly were enrolled in the pre-Omicron or Omicron periods. As observed in EPIC-HR, viral RNA levels for individual subjects with post-treatment viral RNA rebound in EPIC-SR showed no obvious differences in the patterns or magnitude of viral RNA rebound between PAXLOVID and placebo recipients, either overall or within the 2021/pre-Omicron or 2022/Omicron enrollment periods. PAXLOVID treatment also did not result in delayed declines in viral RNA to unquantifiable levels; at all analysis visits through Day

14, and in both the 2021/pre-Omicron and 2022/Omicron periods, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ.

Figure 16 summarizes the rates of post-treatment viral RNA rebound observed in EPIC-HR (conducted during the 2021/pre-Omicron period), EPIC-SR (2021/pre-Omicron period), and EPIC-SR (2022/Omicron period). While there are some modest numeric differences in some comparisons, in general, overall similar rates of post-treatment viral RNA rebound were observed between both trials, between the 2021/pre-Omicron and 2022/Omicron periods, and between PAXLOVID and placebo recipients.

Figure 16. Rates of Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) Observed in EPIC-HR and EPIC-SR



Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
Note: p-values based on Fisher's exact test, two-sided.
Abbreviation: LLOQ, lower limit of quantification; RNA, ribonucleic acid

See Section 18.1 of the integrated review document for additional details from these analyses.

Analyses of Symptom Rebound and Combined Symptom/Viral RNA Rebound in EPIC-HR and EPIC-SR

As with viral RNA rebound, calculated rates of symptom rebound can vary widely depending on the analysis parameters and available data timepoints. In EPIC-HR and EPIC-SR, multiple targeted symptoms were evaluated and there were differences between subjects in baseline symptom duration/severity.

Analyses of symptom rebound focused on symptom rebound after achieving at least a short-term symptom recovery, using the patient eDiary symptom data. Refer to Section 6.2.1.4 for a complete list of all 11 targeted symptoms.

The definitions listed below were used in the symptom rebound analyses.

- **Short Symptom Recovery:** The first day of at least two consecutive diary entries (regardless of missing entries in between) where all targeted symptoms are absent. If a hospitalization event occurs prior to the short symptom recovery day or during the first two short symptom

recovery entries, this subject is considered as not having short symptom recovery through Day 28.

- **Symptom Rebound:** After achieving short symptom recovery, the first day of at least two consecutive diary entries (regardless of missing entries in between) where there is any targeted symptom (regardless of severity), or if a patient is hospitalized or died by Day 28 after short symptom recovery. If a symptom rebound occurred on or before Day 5, the subject is considered not recovered on the day of the symptom rebound and reanalyzed for short symptom recovery and symptom rebound in the following days.
- **Moderate Symptom Rebound:** For those with symptom rebound, having (a) at least one rebound symptom being moderate or severe, (b) at least two symptoms of any severity during a day of rebound, or (c) a hospitalization/death event, observed on a day between the first day of symptom relapse to Day 28.

The analyses were conducted in the mITT2 population for EPIC-HR and the mITT1 population for EPIC-SR (separated by pre-Omicron and Omicron period), including all subjects randomly assigned to study intervention who took at least one dose of study intervention. Subjects with no symptom data are not included. Rates of short symptom recovery, symptom rebound, and moderate symptom rebound are summarized separately for EPIC-HR, EPIC-SR 2021 (pre-Omicron period) and EPIC-SR 2022 (Omicron period) trials in Table 31 below.

Table 31. Symptom Rebound Analysis

Symptom Rebound Analysis	PAXLOVID n (%)	Placebo n (%)
EPIC-HR, N	1031	1050
Short symptom recovery	768 (74.5)	706 (67.2)
Short symptom recovery day ≤ Day 14[a]	546 (53.0)	472 (45.0)
Symptom rebound	90 (11.7)	98 (13.9)
Moderate symptom rebound	54 (7.0)	59 (8.4)
EPIC-SR 2021 (Pre-Omicron), N	534	527
Short symptom recovery [a]	411 (77.0)	404 (76.7)
Short symptom recovery day ≤ Day 14[a]	316 (59.2)	280 (53.1)
Symptom rebound, n[b,c]	65 (15.8)	57 (14.1)
Moderate symptom rebound[b]	40 (9.7)	41 (10.1)
EPIC-SR 2022 (Omicron), N	114	106
Short symptom recovery[a]	96 (84.2)	88 (83.0)
Short symptom recovery day ≤ Day 14[a]	70 (61.4)	68 (64.2)
Symptom rebound, n (%)[b]	10 (10.4)	12 (13.6)
Moderate symptom rebound, n (%)[b]	4 (4.2)	9 (10.2)

Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSL/ADSO datasets, excluding subjects from site HR1274/SR1281, site HR1470/SR1488, site SR1157 (2022), and site SR1197 (2022). Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
[c.] Difference between two arms is not statistically significant: p-value=0.5589 by Pearson chi-squared test with continuity correction.
Abbreviations: N, number of subjects in treatment group; n, number of subjects in specified population or group

These analyses demonstrated that the rates of symptom rebound (regardless of severity) and moderate symptom rebound were similar between PAXLOVID and placebo recipients. Overall symptom rebound rates ranged from 10 percent to 16 percent, with no evidence of a higher rate of symptom rebound or moderate symptom rebound in PAXLOVID recipients relative to placebo recipients in EPIC-HR, the pre-Omicron period of EPIC-SR, or the Omicron period of EPIC-SR. In addition, for either treatment group, there was also no indication of a higher rate of

symptom rebound between the pre-Omicron and Omicron periods of EPIC-SR. Additional subgroup analyses on symptom rebound can be found in Section 16.4.2, with results similar to the above general analysis.

The relationship between viral RNA rebound and symptom rebound could not be fully investigated. The majority of symptom rebounds occurred after Day 14, while viral RNA shedding data were only available through Day 14. Furthermore, viral RNA data were not captured daily, while subject-reported symptoms could vary substantially from day to day. Given these limitations in the combined virology and symptom data, cases of symptomatic viral rebound in EPIC-HR and EPIC-SR were identified based on the following definitions:

- **Combined Recovery**: Those who are virologic responders on Day 5 (<LLOQ at Day 5 or ≥1 $\log_{10}$ copies/mL decline from baseline to Day 5) and have short symptom recovery by Day 14.
- **Symptomatic Viral RNA Rebound**: Among those who have combined recovery, any evidence of viral RNA rebound through Day 14, and have symptom rebound at any time after achieving short symptom recovery.

The analyses were conducted in the mITT2 population for EPIC-HR and the mITT1 population for EPIC-SR (separated by pre-Omicron and Omicron period). Subjects with no symptom data or no viral RNA data are not included. As shown in Table 32, cases of symptomatic viral RNA rebound were infrequent (<2% across both arms) with no consistent trend of a difference in rates between PAXLOVID and placebo recipients in EPIC-HR, and both the pre-Omicron and Omicron periods of EPIC-SR.

Table 32. Symptomatic Viral RNA Rebound Analysis

Symptomatic Viral Rebound Analysis	PAXLOVID n (%)	Placebo n (%)
EPIC-HR, N	1029	1045
Combined recovery [a]	470 (45.7)	385 (36.8)
Symptomatic viral RNA rebound[b]	4 (0.9)	3 (0.8)
EPIC-SR 2021 (Pre-Omicron), N	533	527
Combined recovery[a]	292 (54.8)	232 (44.0)
Symptomatic viral RNA rebound[b]	3 (1.0)	4 (1.7)
EPIC-SR 2022 (Omicron), N	114	106
Combined recovery[a]	62 (54.4)	55 (51.9)
Symptomatic viral RNA rebound[b]	1 (1.6)	0

Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSL/ADMC/ADSO datasets, excluding subjects from site HR1274/SR1281, site HR1470/SR1488, site SR1157 (2022), and site SR1197 (2022). Subjects with no symptom data or no viral RNA data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved combined recovery.
Abbreviations: N, number of subjects in treatment group; n, number of subjects in specified population or group; RNA, ribonucleic acid

Conclusion

Comprehensive analyses conducted by FDA and the Applicant did not identify a clear association between PAXLOVID treatment and COVID-19 rebound. Viral RNA rebound and symptom rebound were observed in both PAXLOVID and placebo recipients, and at frequencies that were generally similar in both arms across multiple analyses, and with no clear differences from analyses of EPIC-HR and the pre-Omicron and Omicron periods of EPIC-SR.

While one analysis from EPIC-HR showed a statistically significantly higher rate of post-treatment viral RNA rebound among PAXLOVID recipients, the review team interprets this difference as minor and not clinically significant. In EPIC-HR, viral RNA rebound was not associated with the primary clinical endpoint of hospitalization or death. There was also no evidence that PAXLOVID treatment was associated with a higher rate of symptom rebound in EPIC-HR; rather, a slightly higher rate of symptom rebound was observed among placebo recipients. Furthermore, regardless of any modest differences in rates of viral RNA rebound, there was no indication of prolonged viral RNA shedding among PAXLOVID recipients. In both EPIC-HR and EPIC-SR (including the pre-Omicron and Omicron periods), a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ at all analysis visits.

Overall, these findings indicate that in a subset of SARS-CoV-2 infections, virologic and/or symptomatic rebound may occur as part of the natural progression and resolution of COVID-19 disease, irrespective of PAXLOVID treatment. Two ongoing clinical trials of PAXLOVID will further characterize the frequency of COVID-19 rebound following different durations of PAXLOVID treatment in immunocompromised subjects (EPIC-IC, NCT05438602) and the potential benefit of PAXLOVID retreatment in subjects with evidence of post-treatment COVID-19 rebound (C4671042, NCT05567952) (ClinicalTrials.gov: NCT05438602 2023; ClinicalTrials.gov: NCT05567952 2023). Both trials are recommended PMCs for inclusion in the Approval Letter, the latter trial to collect efficacy and safety data on a repeat course of PAXLOVID treatment in patients with COVID-19 rebound.

6.3.7. Benefit of PAXLOVID for the Prevention of Post-COVID Conditions

Issue

Does PAXLOVID used to treat acute COVID-19 prevent the development of post-COVID conditions?

Background

Some people infected with SARS-CoV-2 develop new or persistent long-term symptoms after the acute infection resolves. This syndrome is referred to by many names, including post-COVID conditions, long COVID, post-acute sequelae of COVID-19 (PASC), and long haul COVID; we refer to it as post-COVID conditions here. Post-COVID conditions are defined differently by different organizations:

- Per the CDC, post-COVID conditions are an umbrella term for the wide range of health consequences that can be present four or more weeks after infection with SARS-CoV-2, the virus that causes COVID-19 (CDC 2022b).
- Per the World Health Organization (WHO), post-COVID conditions occur in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday

functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time (WHO 2021).

- The WHO clinical case definition was based on a global consensus process whereby patients, patient-researchers, external experts, and WHO staff were asked questions about the definition. For the symptoms, in addition to fatigue, shortness of breath, and cognitive dysfunction, at least 50% of survey respondents thought the following symptoms were important to include: memory issues, post-exertional malaise, sleep disorders, muscle pain/spasms, altered smell or taste, tachycardia/palpitations, cough, chest pain, headache, and joint pain.

The estimated prevalence of post-COVID conditions ranges based on the specific definition used. According to a CDC analysis, 18-19% of American adults who reported ever having had COVID-19 currently have symptoms of post-COVID conditions, defined as symptoms lasting 3 or more months that were not present prior to having COVID-19 (CDC 2022b).

There are many different theories about the etiology behind post-COVID conditions. Proposed contributing mechanisms include persistent inflammation, induced autoimmunity, microvascular dysfunction, dysbiosis, reactivation of latent viruses like human herpes viruses, and persistent SARS-CoV-2 infection (possibly limited to specific anatomic reservoirs) (Mehandru and Merad 2022; Peluso and Deeks 2022). Because treatment of the acute infection could theoretically impact all of the proposed contributing mechanisms for post-COVID conditions, one outstanding question is whether PAXLOVID (or other antiviral) treatment of acute SARS-CoV-2 infection can prevent the development of post-COVID conditions. In addition, the possibility that persistent SARS-CoV-2 infection may contribute to post-COVID conditions has raised interest in studying PAXLOVID for the treatment of individuals diagnosed with post-COVID conditions. However, the role of PAXLOVID in the treatment of post-COVID conditions is beyond the scope of this NDA review as data to assess this were not included in the NDA submission; several clinical trials to evaluate PAXLOVID for the treatment of post-COVID conditions are currently planned or ongoing.

Assessment

While the PAXLOVID clinical trials submitted in support of this NDA were not designed to assess for the development of post-COVID conditions, subjects were queried about the presence of certain symptoms at Week 12 and Week 24, and these data from EPIC-HR were submitted. A comparison of these symptoms in PAXLOVID versus placebo recipients was not a prespecified analysis and was not included as part of the statistical testing hierarchy; however, descriptive analyses of these Week 12 and Week 24 symptom data are presented in Table 33.

The symptoms included in the Week 12 and Week 24 assessments were: cough, shortness of breath, difficulty breathing, fever, chills, fatigue, malaise, muscle pain, diarrhea, nausea, vomiting, headache, sore throat, rhinorrhea, loss of taste/smell, difficulty with concentration, sleep disturbances, and heart palpitations. FDA analysis was limited to the symptoms from the post-COVID conditions WHO clinical case definition that ≥50% of survey respondents thought were important to include (see "Background" at the top of Section 6.3.7), and like terms were grouped. Chest pain and joint pain, which were among the symptoms for the WHO definition

that ≥50% of survey respondents thought were important to include, were not assessed in EPIC-HR at Week 12 and Week 24 and so were not included among the assessed symptoms.

Overall, symptoms associated with post-COVID conditions were infrequent and reported at similar rates among both PAXLOVID and placebo recipients at Week 12 and Week 24 (see Table 33 below).

Table 33. Presence of Symptoms Associated With Post-COVID Conditions at Week 12 and Week 24 Among PAXLOVID and Placebo Recipients in EPIC-HR, mITT1 Analysis Set

	Week 12		Week 24	
Symptoms of Post-COVID-Associated Condition – n (%)	**PAXLOVID (N=929)**	**Placebo (N=919)**	**PAXLOVID (N=918)**	**Placebo (N=916)**
Any of the below symptoms	59 (6%)	69 (8%)	35 (4%)	34 (4%)
Fatigue/malaise	20 (2%)	36 (4%)	17 (2%)	17 (2%)
Shortness of Breath/ Difficulty Breathing	7 (1%)	10 (1%)	4 (<1%)	3 (<1%)
Difficulty with concentration[a]	8 (1%)	11 (1%)	4 (<1%)	4 (<1%)
Sleep disturbance[a]	12 (1%)	14 (2%)	6 (1%)	12 (1%)
Myalgia	1 (<1%)	8 (1%)	1 (<1%)	2 (<1%)
Loss of taste/smell[b]	12 (1%)	10 (1%)	5 (1%)	4 (<1%)
Palpitations[a]	2 (<1%)	11 (1%)	1 (<1%)	7 (1%)
Cough	13 (1%)	12 (1%)	7 (1%)	2 (<1%)
Headache	10 (1%)	18 (2%)	7 (1%)	10 (1%)

Sources: EPIC-HR ADSY dataset, excluding subjects enrolled at Sites 1274 and 1470.
[a.] Due to missing data, for these symptoms at the Week 12 timepoint N=907 and 893 for PAXLOVID and placebo recipients, respectively.
[b.] Due to missing data, N=929 for PAXLOVID at Week 12 for loss of taste/smell.
Abbreviations: COVID, disease caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent-to-treat; N, number of subjects in treatment group

Conclusion

While EPIC-HR did not demonstrate a reduction in symptoms associated with post-COVID conditions at Week 12 and Week 24, these post hoc assessments were not designed to assess for the development of post-COVID conditions and only provide a snapshot of symptoms at two discrete time points. An important limitation of this analysis is that persistence of symptoms for two months or longer is part of the WHO definition for post-COVID conditions, and the existing data did not assess duration of symptoms.

A recent large retrospective cohort study using the U.S. Department of Veterans Affairs healthcare database (N=9217 PAXLOVID recipients versus N=47,123 untreated controls with SARS-CoV-2 infection) suggested that PAXLOVID may reduce the risk of post-COVID conditions; however, this study did not provide sufficient details on the data source, methods, or analytical approach for a thorough review (Xie et al. 2022). Based on the limited information reported in the publication, significant design concerns were identified. The study did not report the validity of their code-based algorithm to capture individual components of "post-COVID conditions." The study also did not capture, nor account for important confounders (e.g., use of certain medications that could influence the risk of the individual clinical condition that consists of "post-COVID conditions") in their analyses.

More data are needed to assess whether PAXLOVID has a role in the prevention of post-COVID conditions.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nirmatrelvir

Nonclinical safety studies with nirmatrelvir included good laboratory practice (GLP) repeat-dose toxicology studies in rats and dogs; developmental and reproductive toxicology studies in rats and rabbits; and in vitro and in vivo safety pharmacology and genotoxicity studies. Overall, the nonclinical safety assessment for nirmatrelvir is considered acceptable to support approval from a pharmacology/toxicology perspective. Exposure multiples mentioned in the summary text are based on total nirmatrelvir concentration. All pertinent studies and findings are summarized in the following section. Full reviews for all nonclinical safety studies are located in Section 13.

Safety Pharmacology

Safety pharmacology studies with nirmatrelvir were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Oral administration of up to 1000 mg/kg of nirmatrelvir to male rats produced no effects on functional observatory behavior (FOB) parameters, but nirmatrelvir (at 1000 mg/kg) administration resulted in transient locomotor effects, as evidenced, during a 60-minute observation session composed of twelve 5-minute intervals, by a lower number of mean vertical movement counts during the first 5-minute period and a higher number of mean horizontal and vertical movement counts during the last 30-minute period. Administration of 1000 mg/kg of nirmatrelvir also resulted in transient respiratory effects (higher respiratory rate and minute volume) compared to vehicle control animals. The central nervous system (CNS) and respiratory effects occurred at systemic exposures approximately 12 times higher than clinical exposure at the proposed human dose of nirmatrelvir 300 mg twice daily.

In a cardiovascular safety pharmacology study in cynomolgus monkeys, small transient effects such as increased systolic, diastolic, and mean blood pressure (BP), heart rate (HR) decreases, and associated RR, PR, and QT interval increases were observed following oral administration of 150 (75 BID) mg/kg/day nirmatrelvir. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. Nirmatrelvir at 150 (75 BID) mg/kg/day also produced slight decreases in cardiac contractility. All measures returned to vehicle control levels within 24 HPD (hours post first dose). Nirmatrelvir-related cardiovascular findings in monkeys were observed at systemic exposure about 2 times higher than clinical exposure at the proposed human dose of 300 mg twice daily. Several in vitro assays, including a hERG assay, and ex vivo studies in perfused heart and aorta, were conducted to assess for potential effects of nirmatrelvir on cardiovascular function and reported negative findings.

The potential effects on CNS, cardiovascular and respiratory safety pharmacology parameters had no correlating clinical signs or histopathological findings in the 14-day or 15-day repeat-dose toxicity studies in rats or monkeys. ECG data were also collected in the 15-day monkey toxicology study, and there were no test article-related changes in ECG parameters (HR, RR, PR, QRS, QT, QTc intervals) or ECG morphology in that study.

General Toxicology

Pivotal repeat-dose toxicology studies were conducted in rats (2-week and 1-month durations) up to 1000 mg/kg/day and in monkeys (15-day and 1-month durations) up to 600 mg/kg/day. All the findings discussed below are considered drug-related but non-adverse. The highest doses tested in pivotal toxicity studies were identified as the no observed adverse effect levels (NOAELs).

Reversible hematological effects were noted in rats and monkeys. In the 14-day repeat dose oral study in rats, there were dose-dependent prolongations in prothrombin time (PT) and activated partial thromboplastin time (aPTT). At the high dose, higher platelet counts in both sexes and lower hemoglobin (HGB) in females were observed. Similar reversible coagulation findings (i.e., increase in platelets and prolongation in PT) were found in the 1-month repeat-dose oral rat study. The hematology and coagulation findings had no clinical or microscopic correlates, and all findings were completely recovered at the end of the recovery phase. In monkeys exposed orally to nirmatrelvir for 15-day and 1-month periods, increases in fibrinogen (FIB), compared with baseline (pre-dose) values, were observed in both sexes at the high dose without correlating histopathological findings. FIB was similar to baseline values at the end of the recovery phase.

In the one-month repeat dose study in monkeys, increased ALT and AST were noted in both sexes at the high dose. Neither macroscopic nor microscopic findings were noted in liver. In the recovery animals, no nirmatrelvir-related changes in clinical pathology parameters were observed.

In both the 14-day and 1-month repeat dose oral study in rats, minimal to mild periportal hepatocellular hypertrophy in both sexes with concomitant increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at the high dose were noted. These microscopic observations were associated with higher mean liver weights and enlarged liver size in males and females at high dose. The hepatocellular hypertrophy was consistent with microsomal enzyme induction. In the thyroid, follicular cell hypertrophy (minimal to mild) was noted in both sexes at high dose in the 14-day study and was noted of all dose groups in the 1-month study. In the 1-month study, but not the 14-day study, minimal to mild cytoplasmic vacuolation in the pituitary gland was noted in the endocrine cells of the pars anterior (males only) at all dose groups. At the end of the recovery phase, in the 14-day study, there were no liver weight differences in either sex. Microscopic changes in the liver and thyroid had completely resolved, indicating full recovery of the dosing phase effects. In the 1-month study, microscopic changes in the liver, thyroid gland, and/or pituitary gland completely recovered at all doses in females and at the low and mid-doses in males, and partially recovered (lower incidence and/or severity) at recovery in males at the high dose of 1000 mg/kg/day. The macroscopic liver findings were completely resolved in both sexes by the end of the 2-week recovery phase. The liver (minimal to mild periportal hepatocyte hypertrophy and vacuolation), thyroid gland (follicular cell hypertrophy) and pituitary gland (vacuolation in the endocrine cells of pars anterior, males only) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone catabolism, a mechanism that rats are known to be particularly sensitive to relative to humans.

Genotoxicity and Carcinogenicity

Nirmatrelvir was negative for mutagenesis in the in vitro reverse mutation assay, negative for clastogenicity in the in vitro assay using human peripheral lymphocytes, and negative for

genotoxicity in the in vivo micronucleus assay in rats exposed up to 1000 mg/kg/day for 14 days. Additionally, a potential impurity (b) (4) was tested in an Ames test for mutagenesis. Overall, the weight of evidence indicates that nirmatrelvir does not exhibit genotoxic potential.

The carcinogenicity potential of PAXLOVID was not evaluated due to the short treatment duration.

Developmental and Reproductive Toxicology

In a fertility and early embryo developmental (FEED) study in rats, nirmatrelvir was orally administered up to 1000 mg/kg/day, no effects on male systemic toxicity or mortality, clinical observations, or effects on food consumption in females were observed. Although epididymal sperm maturation was not reported, no drug-related abnormalities were observed on male reproductive organs upon macroscopic examination. In females, non-adverse increase in body weights were observed at 1000 mg/kg/day prior to mating. No effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. The no observed effect level (NOEL) for male and female fertility (and systemic toxicity) was 1000 mg/kg/day.

In an embryo-fetal developmental study in rats, nirmatrelvir administered orally up to 1000 mg/kg/day was not associated with maternal or fetal effects, including fetal body weights and fetal external, visceral, or skeletal morphology. The maternal and developmental NOAEL was the high dose of 1000 mg/kg/day. In an embryo-fetal development study in rabbits, no maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. However, lower (9%) fetal body weight was observed at the high dose (1000 mg/kg/day). Based on the lack of nirmatrelvir-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day, based on lower fetal body weights at 1000 mg/kg/day.

Rats were administered nirmatrelvir orally at doses of up to 1000 mg/kg/day in a pre- and postnatal developmental (PPND) study. No adverse effects were observed in pregnant rats and offspring at all dose levels. Body weight gain was decreased from PND 10 to 17 in the offspring at the highest dose of 1000 mg/kg/day, resulting in decreased (8% in both males and females compared to controls) body weight at PND 17. No significant difference in body weight was noted at PND 28 (males) or PND 22 (females) to PND 56 (both sexes) and afterwards. The maternal NOAEL was identified at 1000 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day due to an 8% decrease in body weight at PND 17. Drug concentrations in maternal and offspring plasma and breastmilk were not determined.

Additional Toxicology Studies

In an impurity qualification study, nirmatrelvir was administered by oral gavage once daily for 14 days to male and female Wistar Han rats at a dose of 200 mg/kg/day with increased amounts of multiple impurities (b) (4) or (b) (4) or without increased impurities. Non-adverse findings in coagulation, clinical chemistry parameters and liver weight are not different between groups with or without increased impurities. The impurity levels in nirmatrelvir at the NOAEL of 200 mg/kg/day are considered qualified.

Exposure Multiples

Exposure multiples (Table 34) are based on nirmatrelvir predicted systemic exposure ($AUC_{0\text{-}24h}$) in humans at the recommended dosing regimen.

Table 34. Exposure Margins Based on NOAEL of Nirmatrelvir

Study	NOAEL	Adverse Findings	$AUC_{0\text{-}24hr}$[1] (ng·h/mL)	Exposure Multiple[2]
Repeat-Dose Studies (Oral)				
14-day rat	1000 mg/kg	Rats specific liver-thyroid effects due to thyroid hormone metabolism changes, not human relevant.	292,000	4.8
15-day monkey	600 mg/kg	None	1220,000	20.1
Repeat-Dose Studies (Oral)				
1-month rat	1000 mg/kg	Rats specific liver-thyroid-pituitary effects due to thyroid hormone metabolism changes, not human relevant.	548,000	9.0
1-month monkey	600 mg/kg	None	991,000	16.3
Reproductive Toxicology Studies				
Fertility and Early Embryonic Development				
Rat	1000 mg/kg	None	548,000[3]	9.0
Embryo-Fetal Development				
Rat	1000 mg/kg	None	535,000	8.8
Rabbits	300 mg/kg (NOEL)	None	195,000	3.2
	1000 mg/kg	Lower fetal body weight	689,000	11.3
Pre- and Postnatal Development				
Rat	300 mg/kg (NOEL)	None	346000[4]	5.9
	1000 mg/kg	Decreased body weight at PND 17	535,000[4]	8.8

Source: Reviewer assessment based on Studies 20GR276, 20GR289, 21GR122, 21GR125, 21GR146, 21GR132, 21GR126, and 21GR149.
1. $AUC_{0\text{-}24h}$ values for male and female animals combined unless otherwise stated.
2. Based on AUC_{24hr} 60.8 µg.hr/mL in humans at the proposed dosing regimen.
3. No AUCs in this FEED study were reported. Rats AUC24 were estimated based on the 28-day repeat dose study at 1000 mg/kg/day.
4. No AUCs in this PPND study were reported. Rats AUC24 were estimated based on the EFD rat study 28-day repeat dose study at 300 or 1000 mg/kg/day, respectively.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; FEED, fertility and early embryonic development; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PPND, pre- and postnatal development

Ritonavir

Based on the review of NDA-22417 (Ritonavir), which was approved in 1996, one-month repeat-dose oral toxicity studies were conducted in rats and dogs. Liver hepatocyte hypertrophy and periportal inflammation, hypertrophy of thyroid follicular epithelium, and retinal hypertrophy were reported in rats, while liver weight increase, thymus weight decrease. and GI tract distress were noted in dogs. Reproductive studies reported no fertility or reproductive effects in rats. An embryo-fetal developmental study in rats reported reduced fetal weight, delayed skeletal ossification, wavy ribs, enlargement of fontanelles, and cryptorchidism

(See footnote 4 in Table 35) at doses that are maternally toxic. In a fetal and developmental study in rabbits, slight developmental toxicity (reduced fetal size and weight) was noted at dosage that was maternally toxic. No neonatal toxic effects were noted in a pre- and postnatal developmental study in rats.

Exposure Multiples

Exposure multiples (Table 35) are summarized based on the data from the pharmacology review of Ritonavir in 1995.

Table 35. Exposure Margins Based on NOAEL of Ritonavir

Study	NOAEL	Adverse Findings	$AUC_{0\text{-}24hr}$[1] (ng·h/mL)	Exposure Multiple[2]
Repeat-Dose Studies (Oral)				
1-month rat	15 mg/kg	Increase in liver and thyroid weight, periportal inflammation and hepatocyte hypertrophy in liver, thyroid follicular hypertrophy, retinal hypertrophy.	4500	1.3
1-month dog	50 mg/kg	Increase in liver enzymes and weights, decrease in thymus weight, GI distress	17100	5.0
Reproductive Toxicology Studies				
Fertility and Early Embryonic Development				
Rat	75(f)/125(m) mg/kg	No effect on fertility and reproductive performance.	90500 (f)/ 61000 (m)	26.5 (f) / 17.9 (m)
Embryo-Fetal Development				
Rat	15 mg/kg (NOEL)	None	17300	5.1
	35 mg/kg	Reduced fetal weight, delayed skeletal ossification, wavy ribs, enlargement of fontanelles and slight increase in cryptorchidism[4] at maternal toxic doses	34300	10.1
Rabbits	50 mg/kg (NOEL)	None	28550	8.4
	110 mg/kg	Slight reduction in fetal weight and size at maternal toxic dose	Not reported	Not Available
Pre- and Postnatal Development				
Rat	60 mg/kg	None	Not Available[3]	Not Available[3]

Source: Reviewer assessment based on NDA 22417.
[1.] $AUC_{0\text{-}24h}$ values for male and female animals combined unless otherwise stated.
[2.] Based on AUC_{24hr} 3414 ng*hr/mL in humans at the proposed dosing regimen (data from trials under Protocol C4671014).
[3.] No AUCs in this PPND study were reported.
[4.] The interpretation of cryptorchidism in this study is difficult to access because it is not clear how the descent of fetal testes was noted. Typically, the descent of rat testes occurs post-natally (around post-natal day (PND) 15 and completes by PND 40).
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 hours; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PPND, pre- and postnatal development

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Nirmatrelvir is a first-in-class drug, no previously described clinical experience is available to inform any specific safety concern regarding M^{pro} inhibitors.

Ritonavir was approved in the United States in 1996 and is indicated as chronic use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Ritonavir has potential safety concerns which include risk of serious adverse reaction due to drug interactions, toxicity in preterm neonates, hepatotoxicity, pancreatitis, allergic reactions/hypersensitivity, PR interval prolongation, increased concentrations of total cholesterol and triglycerides, diabetes mellitus/hyperglycemia, immune reconstitution syndrome, redistribution/accumulation of body fat, increased bleeding in patients with hemophilia, and development of resistance by HIV-1 to protease inhibitors. In clinical trials, the most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, and abdominal pain), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia (AbbVie 2010).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Safety Concerns Identified Through Emergency Use Authorization

The PAXLOVID EUA outlines mandatory reporting of all medication errors and serious adverse events (SAEs) considered to be potentially related to PAXLOVID. Over 11 million patients worldwide have received PAXLOVID for the treatment of COVID-19 since it was first authorized for emergency use in December 2021, including over 8 million patients in the United States. AEs following use of PAXLOVID that were reported to the FDA Adverse Events Reporting System, the FDA American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Subregistry, and the medical literature have been reviewed regularly by the Office of Surveillance and Epidemiology (OSE) to detect new safety signals.

Based on the review of EUA data, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise are recommended to be included in (b) (4) the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[3] Routine pharmacovigilance will be in place to detect postmarketing signals.

[3] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

7.3.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 2/3 trial populations. The eligibility criteria for EPIC-HR, EPIC-SR, and EPIC-PEP may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.

7.4. FDA Approach to the Safety Review

Adequacy of Applicant's Clinical Safety Assessments

The review team identified a major data reliability issue during the NDA review. Briefly, unusual patterns of viral RNA shedding levels, viral sequencing results, and/or daily clinical symptom reporting times from subjects at four selected study sites in EPIC-HR and EPIC-SR were identified. The FDA approach to the safety review excluded those sites. Two clinical trial sites from EPIC-PEP matching the four EPIC-HR and EPIC-SR sites were also excluded. For further details please refer to Section 6.3.1.

No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in EPIC-HR, EPIC-SR, and EPIC-PEP were coded according to version 24.1 and reviewed and were found to be acceptable. For definitions of AEs, treatment-emergent adverse events (TEAEs), adverse drug reactions, and serious adverse events (SAEs), please see Section 17.1.

Severity grades of AEs were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017) (RSC 2017). Laboratory abnormalities were assessed by threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).

EPIC-HR and EPIC-SR included analyses through Day 34 and EPIC-PEP included analyses through Day 38.

Approach to FDA Assessment of Clinical Trial Data

The FDA review approach for assessment of risk consisted of evaluation of the safety data from the Phase 2/3 trials separately (EPIC-HR, EPIC-SR, and EPIC-PEP) as well as the pooled safety data from EPIC-HR and EPIC-SR. Due to differences of treatment duration, EPIC-PEP (where the treatment duration was either 5 or 10 days) was reviewed separately from EPIC-HR and EPIC-SR (where the treatment duration was 5 days). Results of individual trials are highlighted where important differences may have emerged.

Given the data reliability issues as detailed in Section 6.3.1, subjects at sites 1274 and 1470 (including those switched to 1276) in EPIC-HR, at sites 1281 and 1488 (including those switched to 1282) in EPIC-SR, and at sites 1281 and 1483 (including those switched to 1311) in EPIC-PEP were excluded from the safety analysis.

Safety data from EPIC-HR and EPIC-SR were pooled as both trials represent a 5-day treatment regimen in patients with symptomatic COVID-19. These trials were also analyzed independently

as well given the population differences. EPIC-HR investigated treatment in non-hospitalized symptomatic adult subjects with COVID-19 who were unvaccinated and at increased risk of progressing to severe illness, while EPIC-SR enrolled non-hospitalized symptomatic adults with COVID-19 who were at standard risk of progressing to severe disease (i.e., vaccinated subjects with one or more risk factors for severe COVID-19 and unvaccinated subjects without risk factors for severe COVID-19). Safety data were also analyzed from subjects with at least one risk factor for progression to severe COVID-19 and who were vaccinated in EPIC-SR. Additionally, safety data were analyzed from EPIC-PEP in both 5 and 10-day treatment durations, which investigated a post-exposure prophylaxis regimen in adult household contacts of an individual with symptomatic COVID-19.

Clinical trial data from EPIC-HR, EPIC-SR, and EPIC-PEP were independently analyzed using JMP and JMP Clinical software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. Prespecified hypothesis testing was not proposed for safety outcomes in EPIC-HR, EPIC-SR, and EPIC-PEP. Comparisons are therefore based on descriptive analyses.

It is recommended that Section 6.1 of the label, 'Adverse Reactions from Clinical Trial Experience', include data from the two PAXLOVID treatment trials, EPIC-HR and EPIC-SR.

7.5. Adequacy of the Clinical Safety Database

Overall, the safety database is adequate to assess the safety of PAXLOVID for the proposed indication, dosage regimen, and patient population. See Table 36 and Table 37. A total of 3608 subjects were exposed to PAXLOVID across 13 clinical trials including four Phase 2/3 trials and nine Phase 1 trials. Across the EPIC-HR, EPIC-SR, and EPIC-PEP trials, 2490 subjects received the proposed PAXLOVID twice daily 5-day regimen. In addition, 911 subjects received PAXLOVID for 10 days in EPIC-PEP. Table 36 and Table 37 summarize the exposure periods for pooled EPIC-HR and EPIC-SR, EPIC-HR, EPIC-SR, and EPIC-PEP. The mean (standard deviation [SD]) duration of the exposure in the pooled EPIC-HR and EPIC-SR trials for the PAXLOVID group was 5 (0.7) days and 5 (0.8) days for the placebo group. In EPIC-PEP, the mean (SD) duration of exposure was 9.9 days (1.3) in the 5-day group[4], 9.8 (1.4) in the 10-day group, and 9.9 (1.2) in the placebo group.

Table 36. Duration of Exposure, Safety Population, EPIC-HR and EPIC-SR[1]

	EPIC-HR		EPIC-SR		Pooled	
Parameter	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)
Duration of treatment, days						
Mean (SD)	5 (0.8)	5 (0.8)	5 (0.7)	5.1 (0.6)	5 (0.7)	5 (0.8)
Median (Q1, Q3)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
Min, Max	1, 6	1, 7	1, 6	1, 6	1, 6	1, 7
Total exposure (person years)	14	14	7	7	22	22

[4] Subjects in the 5-day group in EPIC-PEP received five days of PAXLOVID followed by five days of placebo.

	EPIC-HR		EPIC-SR		Pooled	
Parameter	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)
Patients treated, by duration						
≥1 to <3 days	26 (2.5)	40 (3.8)	13 (2.4)	11 (2.1)	39 (2.5)	51 (3.2)
≥3 to <5 days	26 (2.5)	30 (2.8)	5 (0.9)	5 (0.9)	31 (2.0)	35 (2.2)
≥5 to <7 days	986 (95.0)	981 (93.2)	522 (96.7)	512 (97.0)	1508 (95.6)	1493 (94.4)
≥7 days	0	2 (0.2)	0	0	0	2 (0.1)

Source: adex.xpt and adsl.xpt; Software: R
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Duration of treatment is 5 days.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 37. Duration of Exposure, Safety Population, EPIC-PEP[1]

Parameter	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Duration of treatment, days			
Mean (SD)	9.9 (1.3)	9.8 (1.4)	9.9 (1.3)
Median (Q1, Q3)	10 (10, 10)	10 (10, 10)	10 (10, 10)
Min, Max	1, 12	1, 11	1, 11
Total exposure (person years)	25	25	24
Patients treated, by duration			
<3 days	10 (1.1)	9 (1.0)	9 (1.0)
≥3 to <5 days	8 (0.9)	9 (1.0)	6 (0.7)
≥5 to <7 days	15 (1.6)	23 (2.5)	17 (1.9)
≥7 to <10 days	9 (1.0)	11 (1.2)	12 (1.3)
≥10 to <12 days	867 (95.1)	859 (94.3)	854 (95.1)
≥12 days	3 (0.3)	0	0

Source: adex.xpt and adsl.xpt; Software: R.
[1.] Duration of treatment is 5 or 10 days.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

Safety results in this section are presented by EPIC-HR and EPIC-SR (Section 7.6.1), EPIC-PEP (Section 7.6.2), and submission-specific safety issues (Section 7.6.3). Additional analyses based on prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID and are not further discussed in this section: please refer to Section 6.3.2 and Section 17.3.

7.6.1. Safety Results, EPIC HR and EPIC-SR

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, EPIC-HR and EPIC-SR

PAXLOVID demonstrated an overall favorable safety profile in the EPIC-HR and EPIC-SR clinical trials (Table 38). The incidences of SAEs, AEs leading to permanent discontinuation of study drug, any TEAE, and severe AEs were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in PAXLOVID-treated subjects.

Table 38. Overview of Adverse Events[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Event Category	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
SAE	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	8 (1.5)	11 (2.1)	-0.6 (-2.2, 1.0)	26 (1.6)	82 (5.2)	-3.5 (-4.8, -2.3)*
SAEs with fatal outcome	0	13 (1.2)	-1.2 (-1.9, -0.6)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	14 (0.9)	-0.9 (-1.3, -0.4)*
Life-threatening SAEs	3 (0.3)	13 (1.2)	-0.9 (-1.7, -0.2)*	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	4 (0.3)	16 (1.0)	-0.8 (-1.3, -0.2)*
AE leading to permanent discontinuation of study drug	21 (2.0)	45 (4.3)	-2.3 (-3.7, -0.8)*	10 (1.9)	5 (0.9)	0.9 (-0.5, 2.3)	31 (2.0)	50 (3.2)	-1.2 (-2.3, -0.1)*
AE leading to dose modification of study drug	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	6 (0.4)	-0.1 (-0.5, 0.3)
AE leading to interruption of study drug	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	6 (0.4)	-0.1 (-0.5, 0.3)
AE leading to reduction of study drug	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
Other	0	0	0 (0, 0)	0	0	0 (0, 0)	0	0	0 (0, 0)
Any AE[4]	228 (22.0)	256 (24.3)	-2.3 (-6.0, 1.3)	126 (23.3)	126 (23.9)	-0.5 (-5.6, 4.6)	354 (22.4)	382 (24.2)	-1.7 (-4.7, 1.2)
Severe and worse	42 (4.0)	103 (9.8)	-5.7 (-7.9, -3.6)*	18 (3.3)	22 (4.2)	-0.8 (-3.1, 1.4)	60 (3.8)	125 (7.9)	-4.1 (-5.7, -2.5)*
Moderate	68 (6.6)	71 (6.7)	-0.2 (-2.3, 1.9)	34 (6.3)	35 (6.6)	-0.3 (-3.3, 2.6)	102 (6.5)	106 (6.7)	-0.2 (-2.0, 1.5)
Mild	118 (11.4)	82 (7.8)	3.6 (1.1, 6.1)*	74 (13.7)	69 (13.1)	0.6 (-3.4, 4.7)	192 (12.2)	151 (9.6)	2.6 (0.4, 4.8)*

Source: adae.xpt; Software: R
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
[4.] Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, EPIC-HR and EPIC-SR

A total of 14 subjects died in EPIC-HR and EPIC-SR through Day 34, all of whom received placebo. Most deaths were caused by COVID-19 or COVID-19 pneumonia (n=12). Listings of all patient deaths from EPIC-HR and EPIC-SR are summarized in Section 17.2.

7.6.1.3. Serious Treatment-Emergent Adverse Events, EPIC-HR and EPIC-SR

Assessment of SAEs occurring in EPIC-HR and EPIC-SR did not reveal patterns to suggest a serious safety risk attributable to PAXLOVID; the majority of the SAEs were related to the disease under investigation (COVID-19) (Table 39). More SAEs occurred in placebo compared to PAXLOVID in EPIC-HR (1.7% in the PAXLOVID group versus 6.7% in the placebo group), in EPIC-SR (1.5% in the PAXLOVID group versus 2.1% in the placebo group), and in the pooled analysis of EPIC-HR and EPIC-SR (1.6% in the PAXLOVID group versus 5.2% in the placebo group). The most common SAEs (≥2 subjects) in the pooled PAXLOVID group were COVID-19 pneumonia (0.6%), COVID-19 (0.1%), and pneumonia (0.1%). These SAEs occurred at higher frequencies in the placebo group when compared to the PAXLOVID group, overall and by individual trial (with the exception of pneumonia in EPIC-HR which occurred at equal frequencies).

One subject in EPIC-HR (Subject (b) (6)) experienced an SAE considered related to study drug by the investigator. This subject was a 48-year-old female with the risk factor of BMI >25 kg/m^2 in the PAXLOVID group and had treatment-related SAEs of chest discomfort, dyspnea, and palpitations on Day 2. PAXLOVID was permanently discontinued on Day 2 and the SAE resolved on Day 5. There were no other SAEs considered related to study intervention by the investigator in EPIC-HR or EPIC-SR.

SAE assessments were similar using FDA Medical Queries (FMQs). For further details please see Section 17.4.

Table 39. Patients With Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Any SAE	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	8 (1.5)	11 (2.1)	-0.6 (-2.2, 1.0)	26 (1.6)	82 (5.2)	-3.5 (-4.8, -2.3)*
Blood and lymphatic system disorders (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Anemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Cardiac disorders (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Gastrointestinal disorders (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Rectal hemorrhage	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
General disorders and administration site conditions (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Chest discomfort	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatobiliary disorders (SOC)	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatic mass	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Infections and infestations (SOC)	11 (1.1)	54 (5.1)	-4.1 (-5.5, -2.6)*	5 (0.9)	11 (2.1)	-1.2 (-2.6, 0.3)	16 (1.0)	65 (4.1)	-3.1 (-4.2, -2.0)*
Abscess	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Pneumonia aspiration	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Atypical pneumonia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
COVID-19	2 (0.2)	7 (0.7)	-0.5 (-1.0, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	8 (0.5)	-0.4 (-0.8, 0.0)
Pneumonia	1 (0.1)	11 (1.0)	-0.9 (-1.6, -0.3)*	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	2 (0.1)	13 (0.8)	-0.7 (-1.2, -0.2)*
COVID-19 pneumonia	7 (0.7)	36 (3.4)	-2.7 (-3.9, -1.5)*	3 (0.6)	8 (1.5)	-1.0 (-2.2, 0.3)	10 (0.6)	44 (2.8)	-2.1 (-3.0, -1.2)*
Injury, poisoning and procedural complications (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Craniocerebral injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Eye injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hand fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Road traffic accident	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Wrist fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Investigations (SOC)	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	4 (0.3)	3 (0.2)	0.1 (-0.3, 0.4)
Hemoglobin decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatic enzyme increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oxygen saturation decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Creatinine renal clearance decreased	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Alanine aminotransferase increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fibrin D dimer increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Metabolism and nutrition disorders (SOC)	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Electrolyte imbalance	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)

System Organ Class Preferred Term	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Colon adenoma	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Nervous system disorders (SOC)	2 (0.2)	0	0.2 (-0.1, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	0	0.2 (-0.0, 0.4)
Brain stem stroke	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Facial paralysis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Osmotic demyelination syndrome	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)	1 (0.1)	18 (1.7)	-1.6 (-2.4, -0.8)*	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	18 (1.1)	-1.0 (-1.6, -0.5)*
Respiratory distress	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Dyspnea	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Hypoxia	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Interstitial lung disease	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Pulmonary embolism	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Acute respiratory failure	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Pneumonitis	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Vascular disorders (SOC)	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypertensive crisis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with adverse event; SOC, system organ class

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, EPIC-HR and EPIC-SR

Rates of discontinuation were generally balanced between PAXLOVID and placebo groups across both trials (Table 40).

Discontinuations due to dysgeusia were higher (≥2 subjects) in the PAXLOVID group in the pooled EPIC-HR and EPIC-SR trials compared to placebo. Assessments of AEs leading to discontinuation were similar using FMQs. For further details please see Section 17.4.

Reference ID: 5179402

Table 40. Patients With Adverse Events[1] Leading to Treatment Discontinuation by Preferred Term, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Any AE leading to discontinuation	21 (2.0)	45 (4.3)	-2.3 (-3.7, -0.8)*	10 (1.9)	5 (0.9)	0.9 (-0.5, 2.3)	31 (2.0)	50 (3.2)	-1.2 (-2.3, -0.1)*
Diarrhea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
Nausea	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	1 (0.2)	0	0.2 (-0.2, 0.5)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
Vomiting	4 (0.4)	2 (0.2)	0.2 (-0.3, 0.7)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
COVID-19	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Pneumonia	0	3 (0.3)	-0.3 (-0.6, 0.0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
COVID-19 pneumonia	1 (0.1)	12 (1.1)	-1.0 (-1.7, -0.4)*	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	14 (0.9)	-0.8 (-1.3, -0.3)*
White blood cell count decreased	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Creatinine renal clearance decreased	2 (0.2)	4 (0.4)	-0.2 (-0.6, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
Glomerular filtration rate decreased	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	0	0 (0, 0)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
Aspartate aminotransferase increased	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Dysgeusia	2 (0.2)	0	0.2 (-0.1, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	0	0.3 (0.0, 0.5)*
Dizziness	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Respiratory distress	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Dyspnea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Acute respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Cough	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypoxia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Interstitial lung disease	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pneumonitis	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs. placebo
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with adverse event; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, EPIC-HR and EPIC-SR

Table 41 includes TEAEs occurring at 0.5% or higher frequency in EPIC-HR and EPIC-SR. The most common TEAEs (≥2% incidence) in the EPIC-HR PAXLOVID group were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group (4.6% and 3.0% versus 0.1% and 1.5%, respectively). The most common TEAEs observed in EPIC-SR were consistent with those observed in EPIC-HR.

Assessment of TEAEs was similar using FMQs. For further details, please see Section 17.4.

Of the AEs considered by the investigator to be related to study drug in EPIC-HR and EPIC-SR, dysgeusia (4.4% in the PAXLOVID group versus 0% in the placebo group in EPIC-HR; 4.4% in the PAXLOVID group versus 0.2% in the placebo group in EPIC-SR) was reported at a higher frequency in the PAXLOVID group compared with the placebo group. For further details, please see Section 17.4.

As stated in Section 7.3, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise have been identified by OSE or the Applicant during use of PAXLOVID under EUA. Details regarding anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions; headache; and hypertension are provided in their respective sections in 7.6.3. In EPIC-HR and EPIC-SR, the TEAEs of abdominal pain, nausea, vomiting, and malaise all occurred infrequently and at similar frequencies when comparing the PAXLOVID and placebo groups. For further details refer to Table 41 and Section 17.4.

Table 41. Patients With Common Adverse Events[1] Occurring at ≥0.5% Frequency, Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term[3]	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[4]
Any AE	228 (22.0)	256 (24.3)	-2.3 (-6.0, 1.3)	126 (23.3)	126 (23.9)	-0.5 (-5.6, 4.6)	354 (22.4)	382 (24.2)	-1.7 (-4.7, 1.2)
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	30 (5.6)	2 (0.4)	5.2 (3.2, 7.2)*	78 (4.9)	3 (0.2)	4.8 (3.7, 5.8)*
Diarrhea	31 (3.0)	16 (1.5)	1.5 (0.2, 2.7)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	53 (3.4)	32 (2.0)	1.3 (0.2, 2.5)*
Myalgia	7 (0.7)	1 (0.09)	0.6 (0.0, 1.1)*	0	0	0 (0, 0)	7 (0.4)	1 (0.06)	0.4 (0.0, 0.7)*
Hypertension	6 (0.6)	2 (0.2)	0.4 (-0.1, 0.9)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	8 (0.5)	4 (0.3)	0.3 (-0.2, 0.7)
Vomiting	12 (1.2)	9 (0.9)	0.3 (-0.6, 1.2)	10 (1.9)	11 (2.1)	-0.2 (-1.9, 1.4)	22 (1.4)	20 (1.3)	0.1 (-0.7, 0.9)
Dyspepsia	4 (0.4)	4 (0.4)	0.0 (-0.5, 0.5)	4 (0.7)	2 (0.4)	0.4 (-0.5, 1.3)	8 (0.5)	6 (0.4)	0.1 (-0.3, 0.6)
Pyrexia	8 (0.8)	7 (0.7)	0.1 (-0.6, 0.8)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	9 (0.6)	8 (0.5)	0.1 (-0.4, 0.6)
Type 2 diabetes mellitus	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	3 (0.6)	1 (0.2)	0.4 (-0.4, 1.1)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
Creatinine renal clearance decreased	14 (1.3)	16 (1.5)	-0.2 (-1.2, 0.8)	5 (0.9)	4 (0.8)	0.2 (-0.9, 1.3)	19 (1.2)	20 (1.3)	-0.1 (-0.8, 0.7)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	18 (1.1)	19 (1.2)	-0.1 (-0.8, 0.7)
Aspartate aminotransferase increased	10 (1.0)	14 (1.3)	-0.4 (-1.3, 0.5)	7 (1.3)	4 (0.8)	0.5 (-0.7, 1.7)	17 (1.1)	18 (1.1)	-0.1 (-0.8, 0.7)
Cough	6 (0.6)	6 (0.6)	0.0 (-0.6, 0.7)	0	1 (0.2)	-0.2 (-0.6, 0.2)	6 (0.4)	7 (0.4)	-0.1 (-0.5, 0.4)
Abdominal pain upper	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)
C-reactive protein increased	10 (1.0)	13 (1.2)	-0.3 (-1.2, 0.6)	3 (0.6)	2 (0.4)	0.2 (-0.6, 1.0)	13 (0.8)	15 (0.9)	-0.1 (-0.8, 0.5)
Hyperkalemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Tachycardia	0	0	0 (0, 0)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Nausea	15 (1.4)	19 (1.8)	-0.4 (-1.4, 0.7)	17 (3.1)	16 (3.0)	0.1 (-2.0, 2.2)	32 (2.0)	35 (2.2)	-0.2 (-1.2, 0.8)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	9 (0.6)	12 (0.8)	-0.2 (-0.8, 0.4)
Dizziness	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	4 (0.7)	6 (1.1)	-0.4 (-1.6, 0.8)	7 (0.4)	11 (0.7)	-0.3 (-0.8, 0.3)
Blood creatine phosphokinase increased	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	4 (0.8)	-0.0 (-1.1, 1.0)	5 (0.3)	9 (0.6)	-0.3 (-0.7, 0.2)
Blood glucose increased	1 (0.1)	7 (0.7)	-0.6 (-1.1, -0.0)*	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Serum ferritin increased	2 (0.2)	6 (0.6)	-0.4 (-0.9, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Alanine aminotransferase increased	17 (1.6)	27 (2.6)	-0.9 (-2.2, 0.3)	13 (2.4)	8 (1.5)	0.9 (-0.8, 2.6)	30 (1.9)	35 (2.2)	-0.3 (-1.3, 0.7)
Blood thyroid stimulating hormone increased	5 (0.5)	7 (0.7)	-0.2 (-0.8, 0.5)	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	7 (0.4)	12 (0.8)	-0.3 (-0.9, 0.2)
Activated partial thromboplastin time prolonged	9 (0.9)	12 (1.1)	-0.3 (-1.1, 0.6)	3 (0.6)	6 (1.1)	-0.6 (-1.7, 0.5)	12 (0.8)	18 (1.1)	-0.4 (-1.1, 0.3)
Fibrin D dimer increased	22 (2.1)	30 (2.8)	-0.7 (-2.1, 0.6)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	28 (1.8)	36 (2.3)	-0.5 (-1.5, 0.5)
COVID-19	3 (0.3)	13 (1.2)	-0.9 (-1.7, -0.2)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	14 (0.9)	-0.7 (-1.2, -0.2)*
Pneumonia	2 (0.2)	15 (1.4)	-1.2 (-2.0, -0.5)*	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	4 (0.3)	20 (1.3)	-1.0 (-1.6, -0.4)*
COVID-19 pneumonia	8 (0.8)	40 (3.8)	-3.0 (-4.3, -1.8)*	4 (0.7)	10 (1.9)	-1.2 (-2.5, 0.2)	12 (0.8)	50 (3.2)	-2.4 (-3.4, -1.4)*

Source: adae.xpt; Software: R
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Coded as MedDRA preferred terms.
[4.] Difference is shown between PAXLOVID and placebo.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA. Medical Dictionary for Regulatory Activities

7.6.1.6. Laboratory Findings, EPIC-HR and EPIC-SR

Overall, laboratory abnormalities in EPIC-HR and EPIC-SR were similar between the PAXLOVID group and placebo group. For Level 3 laboratory abnormalities as assessed by the Safety Standard & Figures Integrated Guide, PT, high (>1.5x ULN) was the only outlier that occurred more frequently (>1%) in the PAXLOVID group (2.0%) when compared to the placebo group (0.7%). This outlier was noted in EPIC-HR only, overall frequencies of this outlier were similar in EPIC-SR (0.6% in the PAXLOVID group and 0.4% in the placebo group). Given the relatively low frequency of this laboratory finding, specific labeling is not recommended for this PT outlier. For a complete listing of laboratory outliers, please see Section 17.5.

7.6.1.7. Assessment of Drug-Induced Liver Injury, EPIC-HR and EPIC-SR

Figure 17 and Table 42 show screening assessments for potential cases of serious drug-induced liver injury (DILI). There were two cases of potential Hy's Law[5] identified, however, one of these cases did not meet the protocol definition as this subject had baseline hepatic enzyme abnormalities as described below. There were no cases of cholestatic drug-induced liver injury. For further details see Section 17.6.

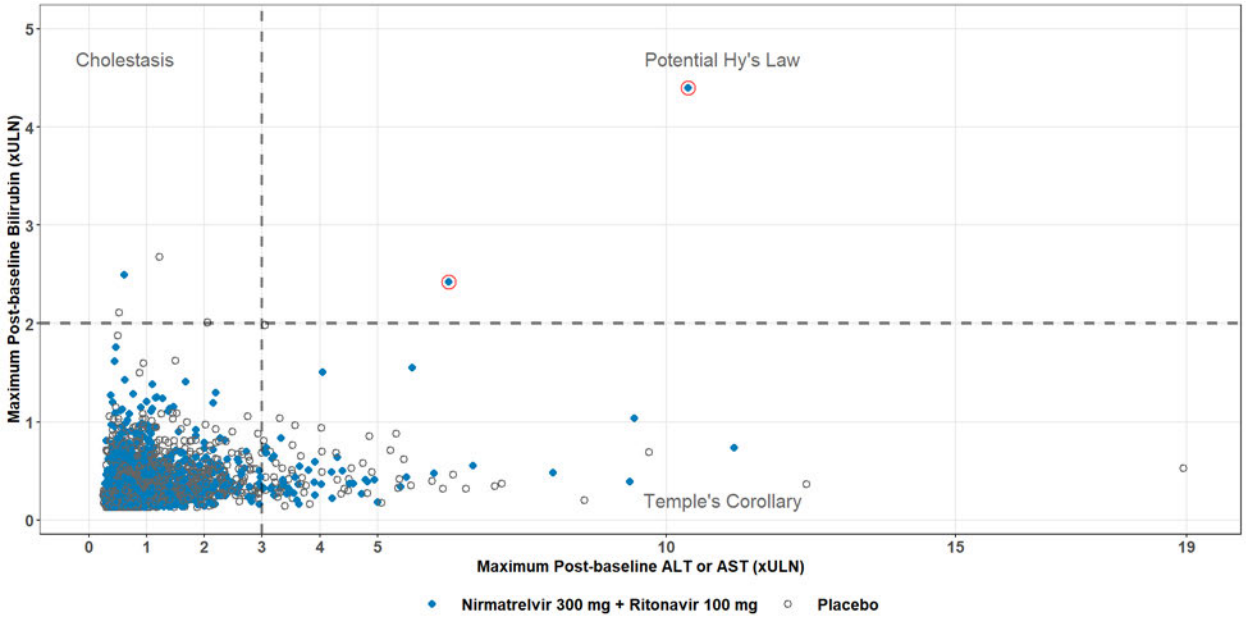
The case of potential Hy's law (EPIC-HR, PAXLOVID group, Subject (b) (6)) occurred during long-term follow-up in a 54-year-old man with hypertension, chronic lung disease, and tobacco use. Liver abnormalities occurred on Day 56 that were in range for potential Hy's Law with both ALT and AST >5x ULN and bilirubin >4x ULN. On the same day it was reported this subject had an AE of moderate (Grade 2) hepatic function abnormality that was not related to study intervention by the investigator and was reported as recovering on Day 168.

Additionally, an event of drug-induced liver injury (EPIC-SR, PAXLOVID group, Subject (b) (6)) occurred in a 31-year-old man who had baseline ALT >13x ULN and bilirubin >3x ULN. These parameters improved on Day 7 and resolved on Day 34. This case did not meet the protocol definition of potential Hy's Law as these abnormalities occurred at baseline. No changes were made to study intervention.

It is unlikely either of these subjects experienced their AEs as a result of study intervention. The laboratory abnormalities noted in Subject (b) (6) were late in follow-up (Day 56), making it unlikely related to study intervention. Subject (b) (6) had the laboratory abnormalities at baseline and improved while on therapy, making it unlikely PAXLOVID contributed to these laboratory abnormalities.

[5] A potential case of Hy's Law was defined as having any postbaseline total bilirubin equal to or exceeding 2x ULN within 30 days after a postbaseline alanine aminotransferase (ALT) or aspartate transaminase (AST) equal to or exceeding 3x ULN and alkaline phosphatase (ALP) <2x ULN.

Figure 17. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-HR and EPIC-SR



Source: adlb.xpt; Software: R
Note: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
Note: A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 42. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR		EPIC-SR		Pooled	
Quadrant	PAXLOVID N=1038 n/N_w (%)	Placebo N=1053 n/N_w (%)	PAXLOVID N=540 n/N_w (%)	Placebo N=528 n/N_w (%)	PAXLOVID N=1578 n/N_w (%)	Placebo N=1581 n/N_w (%)
Potential Hy's Law (right upper)	1/984 (0.1)	0/996 (0)	1/515 (0.2)	0/506 (0)	2/1499 (0.1)	0/1502 (0)
Cholestasis (left upper)	1/990 (0.1)	0/997 (0)	0/519 (0)	3/506 (0.6)	1/1509 (0.1)	3/1503 (0.2)
Temple's corollary (right lower)	38/990 (3.8)	48/997 (4.8)	11/519 (2.1)	14/506 (2.8)	49/1509 (3.2)	62/1503 (4.1)
Total	40/990 (4)	48/997 (4.8)	12/519 (2.3)	17/506 (3.4)	52/1509 (3.4)	65/1503 (4.3)

Source: adlb.xpt; Software: R.
Note: Subjects enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment group; n, number of subjects meeting criteria; N_w, number of patients with data

7.6.1.8. Vital Signs, EPIC-HR and EPIC-SR

Vital signs were analyzed from EPIC-HR and EPIC-SR. There were no clinically relevant changes from baseline or in median values for pulse, respiration rate, or body temperature. For

further details, please see Section 17.7. Systolic and diastolic blood pressures are discussed separately in Section 17.14.3.

7.6.1.9. Subgroups, EPIC-HR and EPIC-SR

In regard to the frequency of TEAEs by demographic subgroups in EPIC-HR, frequencies of SAEs were more frequent in subjects ≥65 years of age (3.1%) when compared to those <65 years of age (1.5%) in the PAXLOVID group. For EPIC-SR this was 2.8% in subjects ≥65 years of age and 1.4% in subjects <65 years of age.

Rates of TEAEs were higher in subjects ≥65-years of age (41.9%) compared to those who were <65 years of age (19.1%) in the PAXLOVID group in EPIC-HR. For EPIC-SR this was 44.4% in subjects ≥65 years of age and 27.8% in subjects <65 years of age. These data are consistent with the epidemiology of COVID-19 subjects where elderly patients are at higher risk for severe disease and adverse outcomes (CDC 2023e; CDC 2023d). No overall safety differences were observed between male and female subjects. No clear significant safety differences were apparent based on race, but the lower enrollment percentages of some racial subgroups preclude definitive conclusions. For further details please see Section 17.8.

7.6.2. Safety Results, EPIC-PEP

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, EPIC-PEP

PAXLOVID demonstrated an overall favorable safety profile in EPIC-PEP (Table 43). The incidences of SAEs, AEs leading to permanent discontinuation of study drug, any TEAE, and severe AEs were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in EPIC-PEP.

Table 43. Overview of Adverse Events[1], Safety Population, EPIC-PEP[2]

Event Category	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
SAE	3 (0.3)	1 (0.1)	2 (0.2)	0.1 (-0.4, 0.6)	-0.1 (-0.5, 0.3)	0.2 (-0.2, 0.6)
SAEs with fatal outcome	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Life-threatening SAEs	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
AE leading to permanent discontinuation of study drug	10 (1.1)	11 (1.2)	14 (1.6)	-0.5 (-1.5, 0.6)	-0.4 (-1.4, 0.7)	-0.1 (-1.1, 0.9)
AE leading to dose modification of study drug	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
AE leading to interruption of study drug	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
AE leading to reduction of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
AE leading to dose delay of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Other	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Any AE	218 (23.9)	212 (23.3)	195 (21.7)	2.2 (-1.7, 6.1)	1.6 (-2.3, 5.4)	0.6 (-3.3, 4.5)
Severe and worse	26 (2.9)	12 (1.3)	16 (1.8)	1.1 (-0.3, 2.5)	-0.5 (-1.6, 0.7)	1.5 (0.2, 2.8)*
Moderate	63 (6.9)	63 (6.9)	60 (6.7)	0.2 (-2.1, 2.5)	0.2 (-2.1, 2.6)	-0.0 (-2.3, 2.3)
Mild	129 (14.1)	137 (15.0)	119 (13.3)	0.9 (-2.3, 4.1)	1.8 (-1.4, 5.0)	-0.9 (-4.1, 2.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Severity as assessed by the investigator.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, EPIC-PEP

There were no deaths reported in EPIC-PEP.

7.6.2.3. Serious Treatment-Emergent Adverse Events, EPIC-PEP

SAEs occurred infrequently in EPIC-PEP across all three groups. The most common SAE was COVID-19 pneumonia (one each in the PAXLOVID 5-day group, PAXLOVID 10-day group, and placebo) which is to be expected as this is the disease under investigation. The remainder of SAEs do not represent concerning safety findings regarding PAXLOVID (see Table 44). SAE assessments were similar using FMQs. For further details please see Section 17.9.

Table 44. Patients With Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, EPIC-PEP[2]

System Organ Class Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Any SAE	3 (0.3)	1 (0.1)	2 (0.2)	0.1 (-0.4, 0.6)	-0.1 (-0.5, 0.3)	0.2 (-0.2, 0.6)
Hepatobiliary disorders (SOC)	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Cholecystitis acute	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Infections and infestations (SOC)	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
COVID-19 pneumonia	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Injury, poisoning and procedural complications (SOC)	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Road traffic accident	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Tibia fracture	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Overdose	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

Source: adae.xpt; Software: R.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, EPIC-PEP

Discontinuation rates were similar and infrequent in all three groups in EPIC-PEP. No patterns of discontinuation from this trial were identified to suggest a serious toxicity concern associated with PAXLOVID (Table 45).

AEs leading to discontinuation assessments were similar using FMQs. For further details please see Section 17.9.

Table 45. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, EPIC-PEP[2]

System Organ Class Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Any AE leading to Discontinuation	10 (1.1)	11 (1.2)	14 (1.6)	-0.5 (-1.5, 0.6)	-0.4 (-1.4, 0.7)	-0.1 (-1.1, 0.9)
Eye disorders (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Eye pain	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Gastrointestinal disorders (SOC)	2 (0.2)	2 (0.2)	0	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	-0.0 (-0.4, 0.4)
Nausea	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
Dyspepsia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
General disorders and administration site conditions (SOC)	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Pain	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Infections and infestations (SOC)	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
COVID-19	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
COVID-19 pneumonia	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Investigations (SOC)	6 (0.7)	4 (0.4)	10 (1.1)	-0.5 (-1.3, 0.4)	-0.7 (-1.5, 0.1)	0.2 (-0.5, 0.9)
Blood urine present	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Activated partial thromboplastin time prolonged	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Aspartate aminotransferase increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Blood fibrinogen decreased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Glomerular filtration rate decreased	1 (0.1)	2 (0.2)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)
Creatinine renal clearance decreased	3 (0.3)	1 (0.1)	4 (0.4)	-0.1 (-0.7, 0.5)	-0.3 (-0.8, 0.2)	0.2 (-0.2, 0.6)
Alanine aminotransferase increased	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
Nervous system disorders (SOC)	3 (0.3)	2 (0.2)	1 (0.1)	0.2 (-0.2, 0.6)	0.1 (-0.3, 0.5)	0.1 (-0.4, 0.6)
Headache	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dysgeusia	2 (0.2)	2 (0.2)	1 (0.1)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	-0.0 (-0.4, 0.4)
Renal and urinary disorders (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Chronic kidney disease	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Respiratory, thoracic, and mediastinal disorders (SOC)	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Cough	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Skin and subcutaneous tissue disorders (SOC)	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)

Source: adae.xpt; Software: R.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of subjects in treatment group; n, number of subjects with at least one event; PT, preferred term; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, EPIC-PEP

Table 46 includes TEAEs occurring at 0.5% or higher frequency in any group in EPIC-PEP. The most common TEAEs (≥2% incidence) in the EPIC-PEP PAXLOVID groups were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group. Similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups. TEAE assessments were similar using FMQs. For further details please see Section 17.9.

Of the AEs considered by the investigator to be related to study drug in EPIC-PEP, dysgeusia (5.9% in the PAXLOVID 10-day group, 6.8% in the PAXLOVID 5-day group versus 0.7% in the placebo group), vomiting (0.7% in the PAXLOVID 5-day group, 0% in the PAXLOVID 10-day group versus 0.1% in the placebo group), and diarrhea (1.2% in the PAXLOVID 5-day group, 1.5% in the PAXLOVID 10-day group versus 0.8% in the placebo group) were reported at a higher frequency in the PAXLOVID group compared with the placebo group. For further details, please see Section 17.9.

As stated in Section 7.3, anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome), and other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise have been identified by OSE or the Applicant during use of PAXLOVID under EUA. Details regarding anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions; headache; and hypertension are provided in their respective sections in Section 7.6.3. In EPIC-PEP, the AEs of abdominal pain, nausea, vomiting, and malaise all occurred infrequently and at similar frequencies when comparing the PAXLOVID and placebo groups. For further details refer to Table 46 and Section 17.9.

Table 46. Patients With Common Adverse Events[1] Occurring at ≥ 0.5% Frequency, Safety Population, EPIC-PEP[2]

Preferred Term[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs. Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Any AE	218 (23.9)	212 (23.3)	195 (21.7)	2.2 (-1.7, 6.1)	1.6 (-2.3, 5.4)	0.6 (-3.3, 4.5)
Dysgeusia	54 (5.9)	62 (6.8)	6 (0.7)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Fibrin D dimer increased	18 (2.0)	13 (1.4)	4 (0.4)	1.5 (0.5, 2.5)*	1.0 (0.1, 1.9)*	0.5 (-0.6, 1.7)
Diarrhea	23 (2.5)	22 (2.4)	15 (1.7)	0.9 (-0.5, 2.2)	0.7 (-0.6, 2.0)	0.1 (-1.3, 1.5)
Nasopharyngitis	13 (1.4)	9 (1.0)	6 (0.7)	0.8 (-0.2, 1.7)	0.3 (-0.5, 1.2)	0.4 (-0.6, 1.4)
Blood fibrinogen decreased	7 (0.8)	5 (0.5)	3 (0.3)	0.4 (-0.2, 1.1)	0.2 (-0.4, 0.8)	0.2 (-0.5, 1.0)
Vomiting	7 (0.8)	3 (0.3)	3 (0.3)	0.4 (-0.2, 1.1)	-0.0 (-0.5, 0.5)	0.4 (-0.2, 1.1)
Creatinine renal clearance decreased	9 (1.0)	5 (0.5)	5 (0.6)	0.4 (-0.4, 1.2)	-0.0 (-0.7, 0.7)	0.4 (-0.4, 1.2)
Nausea	16 (1.8)	12 (1.3)	14 (1.6)	0.2 (-1.0, 1.4)	-0.2 (-1.3, 0.9)	0.4 (-0.7, 1.6)
Upper respiratory tract infection	20 (2.2)	17 (1.9)	18 (2.0)	0.2 (-1.1, 1.5)	-0.1 (-1.4, 1.1)	0.3 (-1.0, 1.6)
Blood thyroid stimulating hormone increased	11 (1.2)	8 (0.9)	10 (1.1)	0.1 (-0.9, 1.1)	-0.2 (-1.2, 0.7)	0.3 (-0.6, 1.3)
Chills	5 (0.5)	0	5 (0.6)	-0.0 (-0.7, 0.7)	-0.6 (-1.0, -0.1)*	0.5 (0.1, 1.0)*
Oropharyngeal pain	7 (0.8)	5 (0.5)	7 (0.8)	-0.0 (-0.8, 0.8)	-0.2 (-1.0, 0.5)	0.2 (-0.5, 1.0)
Blood creatine phosphokinase increased	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Cough	10 (1.1)	2 (0.2)	12 (1.3)	-0.2 (-1.3, 0.8)	-1.1 (-1.9, -0.3)*	0.9 (0.1, 1.6)*
Rhinorrhea	3 (0.3)	5 (0.5)	6 (0.7)	-0.3 (-1.0, 0.3)	-0.1 (-0.8, 0.6)	-0.2 (-0.8, 0.4)
Pyrexia	1 (0.1)	3 (0.3)	6 (0.7)	-0.6 (-1.1, 0.0)	-0.3 (-1.0, 0.3)	-0.2 (-0.6, 0.2)
Aspartate aminotransferase increased	2 (0.2)	5 (0.5)	7 (0.8)	-0.6 (-1.2, 0.1)	-0.2 (-1.0, 0.5)	-0.3 (-0.9, 0.2)
Myalgia	3 (0.3)	2 (0.2)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.8 (-1.5, -0.1)*	0.1 (-0.4, 0.6)
Nasal congestion	4 (0.4)	3 (0.3)	10 (1.1)	-0.7 (-1.5, 0.1)	-0.8 (-1.6, -0.0)*	0.1 (-0.5, 0.7)
Asthenia	10 (1.1)	7 (0.8)	17 (1.9)	-0.8 (-1.9, 0.3)	-1.1 (-2.2, -0.1)*	0.3 (-0.6, 1.2)
Alanine aminotransferase increased	2 (0.2)	6 (0.7)	11 (1.2)	-1.0 (-1.8, -0.2)*	-0.6 (-1.5, 0.3)	-0.4 (-1.0, 0.2)
COVID-19	27 (3.0)	26 (2.9)	36 (4.0)	-1.0 (-2.7, 0.6)	-1.2 (-2.8, 0.5)	0.1 (-1.4, 1.6)
Activated partial thromboplastin time prolonged	11 (1.2)	14 (1.5)	22 (2.4)	-1.2 (-2.5, -0.0)*	-0.9 (-2.2, 0.4)	-0.3 (-1.4, 0.7)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Subjects enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
[4.] Coded as MedDRA preferred terms.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment group; n, number of subjects with adverse event

7.6.2.6. Laboratory Findings, Trial EPIC-PEP

Overall, laboratory abnormalities in EPIC-PEP were similar between the PAXLOVID groups and placebo group. For Level 3 laboratory abnormalities as assessed by the Safety Standard & Figures Integrated Guide, no outliers occurred more frequently (>1%) in the PAXLOVID groups when compared to the placebo group. For a complete listing of laboratory outliers, please see Section 17.10.

7.6.2.7. Assessment of Drug-Induced Liver Injury, EPIC-PEP

In screening analysis for drug-induced liver injury, no subjects met the protocol defined criteria of Hy's Law. For further analyses, please see Section 17.11.

7.6.2.8. Vital Signs' Analyses, EPIC-PEP

Trends in vital signs and body weight in EPIC-PEP were reviewed. There were no clinically relevant changes from baseline or in median values for pulse, respiration rate, or body temperature. For further details please see Section 17.12. Systolic and diastolic blood pressures are discussed separately in Section 7.6.3.4.

7.6.2.9. Subgroups, EPIC-PEP

In regard to the frequency of TEAEs by demographic subgroups in EPIC-PEP, SAEs occurred more frequently in subjects ≥65 years of age when compared to those <65 years of age (for the PAXLOVID 5-day group this was 1.3% in subjects ≥65 years of age versus 0.2% in subjects <65 years of age; for the PAXLOVID 10-day group this was 1.2% subjects ≥65 years of age versus 0% in subjects <65 years of age). This is consistent with the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes (CDC 2023e; CDC 2023d).

Frequencies of TEAEs, however, were similar when comparing subjects ≥65 years of age to those <65 years of age (for the PAXLOVID 5-day group this was 22.8% in subjects ≥65 years of age versus 24.0% in subjects <65 years of age; for the PAXLOVID 10-day group this was 27.7% in subjects ≥65 years of age versus 22.8% in subjects <65 years of age).

No overall safety differences were observed between male and female subjects. No clear significant safety differences were apparent based on race, but the lower enrollment percentages of some racial subgroups preclude definitive conclusions. For further details, please see Section 17.13.

7.6.3. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address submission-specific safety concerns based on nonclinical studies, PAXLOVID clinical experience, and current ritonavir labeling.

7.6.3.1. Thyroid-Related Events

The thyroid was identified as a potential target organ due to microscopic findings in the 14-day GLP rat study with thyroid gland follicular cell hypertrophy. In Trial C4671001, a Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo Controlled, Single- and Multiple-Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of PF-07321332 in Healthy Adult Subjects, clinically meaningful changes in thyrotropin were observed. Three subjects exposed to nirmatrelvir in the multiple ascending dose portion of the trial had abnormal (>1.2x ULN) thyrotropin without changes in free T4 or clinical symptoms. Given these findings, thyroid-related events were added to Adverse Events of Special Interest for EPIC-HR, EPIC-SR, and EPIC-PEP.

No compelling acute phase/inflammatory response signal with PAXLOVID use was identified from the clinical trials. Frequencies of thyroid-related AEs[6] and laboratory outliers (thyrotropin, free thyroxine) were generally infrequent and similar in both PAXLOVID and placebo groups across EPIC-HR, EPIC-SR, and EPIC-PEP.

For further details, please see Section 17.14.1.

No specific labelling is recommended for thyroid events. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.2. Inflammatory Events

In the two pivotal GLP repeat-dose toxicity studies in rats, there was noted to be an increase in white blood cells (due to increases in neutrophils) and decrease in reticulocytes, suggestive of an acute phase/inflammatory response with nirmatrelvir.

No compelling acute phase/inflammatory response signal with PAXLOVID use was identified from the clinical trials. Frequencies of inflammatory-related AEs[7] and laboratory outliers were generally infrequent and similar in both PAXLOVID and placebo groups across EPIC-HR and EPIC-SR. In EPIC-PEP, frequencies of the AE of D-dimer increase were higher in the PAXLOVID groups (2.0% in the 5-day group, 1.4% in the 10-day group) when compared to placebo (0.4%); however, frequencies of the laboratory outlier of D-dimer > 1.5x ULN, however, were similar between the PAXLOVID (8.3% in the 5-day group, 7.0% in the 10-day group) when compared to the placebo group (8.1%). The remainder of inflammatory-related AEs and laboratory outliers were similar between the PAXLOVID and placebo groups in EPIC-PEP. There were no SAEs or deaths in the PAXLOVID-treated groups related to inflammatory events. There was one subject in the PAXLOVID 5-day group in EPIC-PEP who discontinued study

[6] Thyroid-related events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

[7] Inflammatory events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

drug as a result of an inflammatory event. There was one subject in the PAXLOVID 5-day group in EPIC-PEP who discontinued study drug as a result of an inflammatory event [Grade 3 prolonged activated partial thromboplastin time on Day 8 (Subject (b) (6) in EPIC-PEP)]. There were no discontinuations due to inflammatory events in PAXLOVID-treated subjects in EPIC-HR or EPIC-SR.

No specific labelling is recommended for inflammatory events. Routine pharmacovigilance will be in place to detect postmarketing signals.

For further details, please see Section 17.14.2.

7.6.3.3. Hypersensitivity Events

Hypersensitivity is in the current ritonavir label and is currently in the PAXLOVID EUA Fact Sheet (FS) for Healthcare Providers (HCP) under Section 5, “Warnings and Precautions” and Section 6.2, "Post-Authorization Experience” (Pfizer 2023a).

Hypersensitivity events[8] were infrequent and similar in EPIC-HR and EPIC-SR. In the EPIC-HR frequencies of hypersensitivity events were 0.4% in the PAXLOVID group and 0.5% in the placebo group. For EPIC-SR this was 0.4% in the PAXLOVID group and none in the placebo group. There were no SAEs or deaths related to hypersensitivity events. A single PAXLOVID-treated subject discontinued due to a hypersensitivity event [Grade 3 rash on Day 2 (Subject (b) (6) in EPIC-HR)]. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in either EPIC-HR or EPIC-SR.

In EPIC-PEP, hypersensitivity events were infrequent and similar between the two groups: reported in 0.2% of subjects in the PAXLOVID 5-day group, 0.2% of subjects in the PAXLOVID 10-day group and none in the placebo group. There were no hypersensitivity event SAEs or deaths. A single PAXLOVID-treated subject discontinued due to a hypersensitivity event [Grade 1 rash on Day 4 (Subject (b) (6)]. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in EPIC-PEP.

While hypersensitivity events associated with PAXLOVID use were infrequent in EPIC-HR, EPIC-SR, and EPIC-PEP, inclusion of Hypersensitivity Reactions in Warnings and Precautions is recommended to communicate that anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) and other hypersensitivity reactions have been reported with PAXLOVID use (in the EUA setting). In addition, inclusion of hypersensitivity events that have been identified under EUA are recommended in Section 6 of labeling. For further information regarding these reports, please refer to the EUA memos dated February 23, 2022, and September 26, 2022 (FDA 2022a; FDA 2022b).

For further details, please refer to Section 17.14.1.

7.6.3.4. Hemodynamic Events

Hypertension is included in Section 6.1, “Adverse Reactions from Clinical Studies”, of the current EUA FS for HCP (Pfizer 2023a); therefore, an assessment of hemodynamic AEs in the

[8] Hypersensitivity events defined by Applicant using Preferred Terms within the Hypersensitivity Standardized MedDRA Query – MedDRA v 24.1 as detailed in Applicant’s Summary of Safety Appendix 3 (m.2.7.4)

clinical trials was performed. Frequency of hemodynamic AEs[9] were similar between the PAXLOVID groups and the placebo groups in EPIC-HR (0.8% in the PAXLOVID group and 0.8% in the placebo group) and EPIC-SR (1.5% in the PAXLOVID group and 1.5% in the placebo group). There was one SAE and discontinuation related to hemodynamic events in EPIC-HR as detailed below. There were no deaths related to hemodynamic events in EPIC-HR, EPIC-SR, or EPIC-PEP. There were three Grade 3 or higher AEs related to hemodynamic AEs, two in PAXLOVID-treated subjects and one in a placebo-treated subject:

- Subject (b) (6) was a 62-year-old female in the EPIC-HR PAXLOVID group with a history of hypertension and cardiovascular disease. On Day 2, reported SAE of life-threatening (Grade 4) hypertensive crisis. Additionally on Day 2, the subject experienced headache, blurred consciousness, and convulsive seizures. Study intervention was permanently discontinued on Day 2. The event of hypertensive crisis was reported as resolved on Day 14 and the subject was discharged from the hospital on the same day.
- Subject (b) (6) was a 40-year-old male in the EPIC-HR PAXLOVID group who was a current smoker and had a medical history of diabetes mellitus who experienced severe (Grade 3) hypertension on Day 5. Study intervention was permanently withdrawn on Day 3, and on Day 5 the subject was hospitalized with the SAEs of abscess and sepsis. The subject was discharged on Day 9 and the SAEs of abscess and sepsis were resolved on the same day. The event of hypertension was reported as ongoing at time of last available report.
- Subject (b) (6) was a 44-year-old male in the EPIC-HR placebo group who was a current smoker and had a history of hypertension who experienced severe (Grade 3) hypertension on Day 3. The subject was treated with antihypertensives, and no changes were made to study intervention. This AE was reported as resolved on Day 5.

In EPIC-HR and EPIC-SR, the frequencies of systolic blood pressure ≥140 mmHg (19.7% in the PAXLOVID group and 19.1% in the placebo group in EPIC-HR; 18.0% in the PAXLOVID group and 19.2% in the placebo group in EPIC-SR) were similar between the PAXLOVID and placebo groups. Frequencies of diastolic blood pressure ≥90 mmHg (23.4% in the PAXLOVID group and 22.6% in the placebo group in EPIC-HR; 16.9% in the PAXLOVID group and 23.9% in the placebo group in EPIC-SR) were also similar between both groups.

In EPIC-PEP, the AE of hypertension was infrequent and occurred at similar frequencies between the 5-day (0.2%), 10-day (0.2%), and placebo (0.1%) groups. When evaluating vital signs, frequencies of systolic blood pressure >140 mmHg (10.6% in the PAXLOVID 5-day group, 10.5% in the PAXLOVID 10-day group, and 9.9% in the placebo group) and diastolic blood pressure >90 mmHg (11.7% in the PAXLOVID 5-day group, 10.8% in the PAXLOVID 10-day group, and 12.5% in the placebo group) were similar across all groups

For further details, please see Section 17.14.3.

Overall, frequencies of hemodynamic AEs and maximum blood pressures were similar between the PAXLOVID and placebo groups in all three trials with only a single hemodynamic event SAE reported in a PAXLOVID-treated subject. There was no compelling signal detected in the clinical trial data with PAXLOVID use to support labeling for hypertension. Cases of

[9] Hemodynamic events defined by Applicant using Preferred Terms – MedDRA v24.1 as detailed in Applicant's Summary of Clinical Safety Appendix 3 (m.2.7.4)

hypertension identified under the EUA do support labeling, and therefore labeling is recommended to include hypertension given post-marketing findings under Section 6.1, "Emergency Use Authorization Experience in Subjects with COVID-19." For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[10]

7.6.3.5. Dysgeusia

Dysgeusia is a known adverse reaction of ritonavir and is currently in the EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (AbbVie 2010; Pfizer 2023a). Dysgeusia was more common in the PAXLOVID group in EPIC-HR (4.6% in the PAXLOVID group versus 0.1% in the placebo group) and in EPIC-SR (5.6% in the PAXLOVID group versus 0.4% in the placebo group). The majority of dysgeusia in these trials was mild (Grade 1) or moderate (Grade 2) in severity. There were no SAEs related to dysgeusia across both trials. Two PAXLOVID-treated subjects experienced severe (Grade 3) dysgeusia across both trials, including one subject who discontinued study treatment on Day 3.

In EPIC-PEP, dysgeusia occurred at a higher frequency in the PAXLOVID 5-day (5.9%) and 10-day (6.8%) groups when compared to the placebo group (0.7%). The majority of dysgeusia in this trial was mild (Grade 1) or moderate (Grade 2) in severity in EPIC-PEP. There were no SAEs associated with dysgeusia. Two subjects experienced severe (Grade 3 dysgeusia), one each in the 5-day and 10-day groups.

Dysgeusia resulted in discontinuation of study drug in two (0.2%) subjects in the 5-day group, two (0.2%) subjects in the 10-day group, and one subject (0.1%) in the placebo group.

Dysgeusia is a known adverse reaction with ritonavir. Although this was a common adverse reaction, most cases were mild or moderate in severity and few resulted in discontinuation of PAXLOVID. Dysgeusia is recommended for inclusion in Section 6 of the label.

7.6.3.6. Diarrhea

Diarrhea is a known adverse reaction of ritonavir and is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (AbbVie 2010; Pfizer 2023a). In EPIC-HR diarrhea occurred at higher frequency in the PAXLOVID group (3.0%) when compared to the placebo group (1.6%). In EPIC-SR diarrhea was also more frequent in the PAXLOVID group (4.1%) when compared to the placebo group (3.0%). There were no SAEs, no deaths, or severe (Grade 3) or life-threatening (Grade 4) AEs related to diarrhea in either EPIC-HR or EPIC-SR. Three (0.2%) subjects in the pooled PAXLOVID group discontinued study drug as a result of this AE.

In EPIC-PEP, diarrhea was more frequent in the PAXLOVID 5-day group (2.5%) and 10-day group (2.4%) when compared to the placebo group (1.7%). There were no severe or life-

[10] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

threatening AEs of diarrhea, no cases of diarrhea resulting in discontinuation, no SAEs related to diarrhea, and no deaths associated with diarrhea.

Diarrhea occurred at higher frequencies in the PAXLOVID groups when compared to placebo groups in EPIC-HR, EPIC-SR, and EPIC-PEP. Diarrhea is recommended for inclusion in Section 6 of the label.

7.6.3.7. Headache

Headache is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (Pfizer 2023a). In EPIC-HR, headache occurred at similar rates between the PAXLOVID group (1.2%) and placebo group (1.2%). The AE of headache was also similar between the PAXLOVID group (1.1%) and the placebo group (1.1%) in EPIC-SR. All AEs of headache were either mild (Grade 1) or moderate (Grade 2) in severity. There were no SAEs, discontinuations, or deaths associated with the AE of headache in these two trials.

In EPIC-PEP, headache occurred less frequently in the PAXLOVID 5-day group (1.6%) and 10-day group (1.9%) when compared to the placebo group (3.2%). Headache AEs were mild (Grade 1) or moderate (Grade 2) in severity except for one instance of severe (Grade 3) headache in the placebo group. Study drug was withdrawn because of headache in one subject in the PAXLOVID 5-day group and no cases of headache were considered SAEs.

The majority of cases of headache were mild to moderate in severity and few instances led to discontinuation of study drug. In the clinical trials, there was no compelling signal that would support labeling, however, cases identified under the EUA do support labeling. For further details, please refer to the OSE review by Kate McCartan, Maya Beganovic, Toni Salvatore, Irene Rwakazina, Sonal Goyal, Rachna Kapoor, Sheheryar Muhammad, Neha Gada, Sevan Kolejian, Rajdeep Gill, and Ida-Lina Diak for details (DARRTS ID: 5077785 2022).[11] Specific labeling is recommended for inclusion to address headache given postmarketing findings under Section 6.1, "Emergency Use Authorization Experience in Subjects with COVID-19."

7.6.3.8. Myalgia

Myalgia is included in the current EUA FS for HCP under Section 6.1, "Adverse Reactions from Clinical Studies" (Pfizer 2023a). In EPIC-HR, myalgia was infrequent, occurring in 0.7% of subjects in the PAXLOVID group and 0.1% in the placebo group. In EPIC-SR, myalgia occurred in no subjects in either group. There were no myalgia-associated SAEs, discontinuations, or deaths in EPIC-HR and EPIC-SR. There was a single Grade 4 event of blood creatine phosphokinase increased in a PAXLOVID-treated subject (Subject (b) (6), EPIC-SR on Day 1).

In EPIC-PEP, myalgia occurred at similar frequencies in all three groups (0.3% in the PAXLOVID 5-day group, 0.2% in the PAXLOVID 10-day group, and 1.0% in the placebo group). There were no myalgia-associated SAEs, discontinuations, or deaths.

[11] This document contains proprietary data obtained by FDA under contract and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188 and EUA 105. The source can only be accessed by authorized individuals.

Rates of creatine kinase increase was infrequent and similar between PAXLOVID and placebo in EPIC-HR, EPIC-SR, and EPIC-PEP.

While the current EUA FS for HCP includes myalgia, review of EPIC-HR, EPIC-SR, and EPIC-PEP safety data does not identify a compelling signal for myalgia associated with PAXLOVID use. Therefore, myalgia is not recommended for inclusion in product labeling.

7.6.3.9. Hepatoxicity

The liver was considered a potential target organ due to microscopic findings in the 14-day GLP rat study, with findings including minimal to mild periportal hepatocellular hypertrophy and vacuolation in a dose-dependent fashion plus increased liver size and weights. Additionally, hepatotoxicity is currently in the Warnings and Precautions and Adverse Reaction sections of the ritonavir label as well as in the PAXLOVID EUA FS for HCP under "Warnings and Precautions" based on the ritonavir label (AbbVie 2010; Pfizer 2023a).

Comparable frequencies of AEs related to hepatobiliary disorders were reported when comparing the PAXLOVID and placebo groups in EPIC-HR (0.4% in PAXLOVID and 0.2% in placebo) and EPIC-SR (0.2% in PAXLOVID and 0.2% in placebo). No subject with a reported hepatobiliary AE discontinued study drug across all trials. In EPIC-SR, the SAE of hepatic mass was reported in Subject (b) (6) This subject was a 46-year-old female with a risk factor of BMI>25 kg/m^2 but was fully vaccinated. On Day 9 this subject experienced abdominal pain and low-grade fever. On Day 13 this subject was diagnosed with the SAE of moderate (Grade 2) hepatic mass with imaging suggestive of malignancy. On Day 42 this subject underwent colonoscopy and was found to have a sigmoid tumor. This event was not considered related to study intervention by the investigator and did not result in discontinuation of study drug. There were no SAEs related to hepatobiliary disorders in PAXLOVID-treated subjects in EPIC-HR.

In EPIC-HR and EPIC-SR, no cases of Hy's Law were identified in either treatment group through Day 34. There was one case of potential Hy's Law reported in long term follow-up. For further details, please refer to Section 7.6.1.7. In EPIC-PEP, no subjects met the protocol defined criteria of Hy's Law (refer to Section 7.6.2.7).

For further details regarding hepatic laboratory abnormalities, please see Section 7.6.1.6 for EPIC-HR and EPIC-SR and Section 7.6.2.6 for EPIC-PEP.

Overall, hepatobiliary AEs were infrequent in EPIC-HR, EPIC-SR, and EPIC-PEP. Although there was one SAE in the PAXLOVID-treated group in EPIC-PEP, this is unlikely to be related to study drug given the nature of the hepatic mass being related to suspected colon cancer. No specific labeling for these events is recommended; however, hepatotoxicity language in the Warnings and Precautions section, similar to that in the current PAXLOVID EUA FS for HCP, is recommended based on the ritonavir label. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.10. Ritonavir-Specific Labeling

The following are in Section 5, "Warnings and Precautions", of the current Ritonavir label (AbbVie 2010). Drug-drug interaction, hepatotoxicity, and hypersensitivity are covered in other sections of this review and will not be discussed in this section.

7.6.3.10.1. Pancreatitis

No cases of pancreatitis were reported across all three trials: no specific labeling is recommended. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.2. PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients and there have been cases of second- or third-degree atrioventricular block. Electrocardiogram data were collected from the sentinel cohorts of EPIC-HR and EPIC-SR. A PR interval >40 msec change occurred in 1/150 (0.1%) in the pooled PAXLOVID group and 3/201 (1.5%) in the pooled placebo group. There was one subject in the PAXLOVID group with a PR interval >40 msec change (Subject (b) (6) in EPIC-HR), however this was isolated and without associated symptoms.

No specific labeling is recommended. Routine pharmacovigilance will be in place to detect postmarketing signals.

7.6.3.10.3. Lipid Disorders and Fat Redistribution

Treatment with ritonavir alone or in combination with saquinavir has resulted in increases in the concentration of total cholesterol and triglycerides. A single PAXLOVID-treated subject (EPIC-PEP, 5-day group) experienced moderate (Grade 2) hyperlipidemia. Laboratory data regarding lipids were not routinely collected in EPIC-HR, EPIC-SR, and EPIC-PEP.

Lipid-related AEs were infrequently reported in all trials. No labeling for lipid disorders or fat redistribution is recommended. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.4. Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy.

Review of EPIC-HR, EPIC-SR, and EPIC-PEP safety data does not identify a compelling signal for diabetes mellitus or hyperglycemia associated with PAXLOVID use; therefore, no specific product labeling is recommended. For further details please refer to Sections 7.6.1.5, 7.6.1.6, 7.6.2.5, 7.6.2.6. Routine pharmacovigilance will be in place to detect post-marketing signals.

7.6.3.10.5. Immune Reconstitution Syndrome and Resistance/Cross-Resistance

Subjects living with HIV were permitted to be enrolled in EPIC-HR, EPIC-SR, and EPIC-PEP, however, subjects were required to have an HIV viral load less than 400 copies/mL. There only were two subjects living with HIV who received PAXLOVID across all three trials: no AE of immune reconstitution syndrome was reported.

A Warning and Precaution regarding the risk of HIV-1 resistance development is recommended for inclusion in the product label, similar to that in the current PAXLOVID EUA FS for HCP, because nirmatrelvir is co-administered with ritonavir; there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

7.6.3.10.6. Patients With Hemophilia

There have been reports of increased bleeding in patients with hemophilia type A and B treated with protease inhibitors. No individuals with hemophilia were enrolled in EPIC-HR, EPIC-SR, or EPIC-PEP.

7.7. Key Safety Review Issues

7.7.1. Serious Adverse Reactions Due to Drug-Drug Interactions (DDIs)

Issue

What is the overall risk for serious adverse reactions due to DDIs in the PAXLOVID-eligible population and how can this risk best be mitigated?

Background

PAXLOVID is a co-packaged oral drug product comprising nirmatrelvir, a SARS-CoV-2 M^{pro} inhibitor, and ritonavir, a potent CYP3A inhibitor that is included to increase nirmatrelvir plasma levels. The key safety concern related to PAXLOVID is the risk of serious adverse reactions due to DDIs, mainly related to the ritonavir component (see Section 8.2.2). However, because the Phase 3 clinical trials EPIC-HR, EPIC-SR, and EPIC-PEP excluded subjects with current or expected use of any medications that have DDIs with PAXLOVID that may lead to serious AEs, this risk cannot be evaluated through analysis of these clinical trial data.

Ritonavir exhibits near maximal CYP3A inhibition when administered at a dose of 100 mg and can result in significant elevations of concomitant medications that are metabolized by the CYP3A isoenzyme. In the current PAXLOVID EUA FS for HCP, the table of "Established and Other Potentially Significant Drug Interactions" currently lists 143 drugs that have DDIs with PAXLOVID, as well as a statement that the listed drugs are not considered a comprehensive list. The 143 listed drugs include 37 drugs that are contraindicated with PAXLOVID, 21 drugs for which the recommendation is "avoid concomitant use" or "discontinue use prior to initiation of PAXLOVID", 49 drugs for which a dose adjustment is recommended or suggested, and 6 drugs for which therapeutic drug concentration or pharmacodynamic laboratory marker monitoring is recommended. The contraindications and DDIs included in the PAXLOVID EUA FS for HCP mirror those in the concomitant drug labels and the Norvir and HIV boosted protease inhibitor labels, with several additions based on the National Institutes of Health guidelines for DDIs with PAXLOVID (NIH 2023). Of note, drugs that are not contraindicated or listed as "avoid concomitant use" can still lead to clinically significant DDIs if not appropriately managed, such as renal failure (tacrolimus) or fatal respiratory depression (some narcotic analgesics).

Multiple risk-mitigation efforts have been employed by FDA to reduce the risk of serious AEs from PAXLOVID DDIs when used under EUA. The current EUA FS for HCP contains a Warning and Precaution about the risk of serious adverse reactions due to DDIs (Pfizer 2023a). Additional measures include 1) posting of a PAXLOVID Patient Eligibility Screening Checklist and Drug Interaction Tool; 2) five separate updates to the FS for HCP to better describe the DDIs; 3) generation of Dear Healthcare Provider letters communicating the risk of DDIs with PAXLOVID; 4) posting information on how to assess for PAXLOVID DDIs in a FAQ document and Center for Drug Evaluation and Research (CDER) conversation; and 5) presentations by PAXLOVID reviewers and OID leadership at multiple outside talks/webinars provided in conjunction with the AMA, CDC, and ASPR.

Assessment

Analysis of Available Data

As noted above, the risk of serious adverse reactions due to DDIs cannot be assessed through the available clinical trial data because the aforementioned clinical trials excluded subjects on medications with clinically significant DDIs. Consequently, the risk of serious adverse reactions due to DDIs was assessed in three analyses conducted by the OSE regarding post-authorization use of PAXLOVID. These analyses describe:

1. The proportion of the PAXLOVID-eligible population who are taking concomitant medications that have DDIs with PAXLOVID
2. The types of healthcare providers who are prescribing PAXLOVID in the United States
3. The AEs reported that are probably or possibly related to PAXLOVID DDIs with concomitant drugs that are labeled to have potential significant DDIs with PAXLOVID

Proportion of the PAXLOVID-Eligible Population Who Are Taking Concomitant Medications That Have DDIs With PAXLOVID

The PAXLOVID-eligible population, i.e., adults who are at high risk for development of severe COVID-19, are likely to be taking concomitant medications that have DDIs with PAXLOVID. Analyses were performed using the Medicare database from December 22, 2021 to September 10, 2022, the Veterans Affairs (VA) database from January 01, 2022 to October 31, 2022, and the Sentinel Rapid COVID data from December 22, 2021 to December 31, 2022, among adults who had COVID-19 and were eligible for PAXLOVID treatment based on being high risk for severe COVID-19 (due to age ≥65 years or high-risk comorbidities[12]) and not having evidence of severe renal or hepatic impairment. Drugs included in the February 1, 2023 update to the PAXLOVID Fact Sheet for Healthcare Providers were used to determine drugs with PAXLOVID DDIs. (see Section 21.1 for details)

In all three databases, 57-66% of PAXLOVID-eligible adults were on a drug that had DDIs with PAXLOVID at the time of COVID-19 diagnosis, including 7-12% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 29-40% on a drug for which the

[12] High-risk comorbidities include pregnancy, immunosuppressive disease and immunosuppressive treatment, chronic lung diseases (asthma, reactive airway, other chronic respiratory diseases, and chronic obstructive pulmonary disease), cardiovascular disease, hypertension and congenital heart disease, obesity/overweight, chronic kidney disease, diabetes, and sickle cell disease.

PAXLOVID fact sheet recommended "avoid concomitant use", and 40-45% on a drug with DDIs with PAXLOVID with other recommended actions (e.g., dose modification, laboratory monitoring, or clinical monitoring) (Table 234). A similar analysis was performed in the VA and Sentinel databases with a broader definition of high risk for severe COVID-19 (age ≥50 years or high-risk comorbidities); in this analysis of the VA and Sentinel databases, respectively, 56% and 53% of eligible adults were on a drug that had DDIs with PAXLOVID at the time of COVID-19 diagnosis, including 8% and 7% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 34% and 26% on a drug for which the PAXLOVID fact sheet recommended "avoid concomitant use", and 40% and 39% on a drug with DDIs with PAXLOVID with other recommended actions (Table 235).

In all the analyses, the most common drugs with DDIs being taken by PAXLOVID-eligible adults were atorvastatin and amlodipine, and almost all of the 10 most common DDI drugs from each of the analyses could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring (depending on the clinical situation for each particular patient). (Table 237).

One limitation of these analyses is that populations identified in the study data sources may not fully represent the PAXLOVID-eligible U.S. population. With a few exceptions, adults must be ≥65 years of age to be eligible for Medicare, the VA population is disproportionately male and Sentinel Rapid COVID-19 data included only the population covered by a commercial health plan. However, despite these limitations, these analyses indicate that a sizeable proportion of PAXLOVID-eligible adults are taking medications that have DDIs with PAXLOVID.

Types of Healthcare Providers Who Are Prescribing PAXLOVID in the United States

PAXLOVID is prescribed by a broad range of healthcare providers who may not be familiar with ritonavir DDIs. An OSE analysis was done using the Symphony Health Metys™ drug utilization database which provides dispensed prescription estimates from a sample of U.S. outpatient pharmacies, representing approximately 85% of all retail prescriptions, 73% of all mail-order prescriptions, 75% of all specialty prescriptions, and 50% of all long-term care prescriptions, with prescription estimates projected to the national level. From December 25, 2021 to January 13, 2023, most PAXLOVID prescriptions in the United States were from adult primary care practitioners (74% from family medicine, general medicine, or internal medicine) or emergency room practitioners (7%). In contrast, other ritonavir-containing products that are used to treat HIV are generally prescribed by HIV specialists or providers who focus on HIV treatment who may be more experienced with managing ritonavir DDIs.

Adverse Events Reported That Are Probably or Possibly Related to PAXLOVID DDIs With Concomitant Drugs That Are Labeled to Have Potential Significant DDIs With PAXLOVID

OSE analyzed cases of AEs following use of PAXLOVID for the treatment of COVID-19 under EUA that were reported to the FAERS, which accounted for >99% of reported cases), the FACT (FDA-American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium) Pharmacovigilance Project Subregistry, and the medical literature through January

Reference ID: 5179402

30, 2023[13]. OSE identified 301 cases of AEs that they assessed as possibly or probably related to DDIs included in the current EUA FS for HCP. A total of 271 of these cases reported at least one serious outcome, including 147 reporting hospitalization. Six cases reported a fatal outcome after a DDI-related AE (four related to concomitant tacrolimus use, one related to concomitant verapamil use, and one related to concomitant use of both nifedipine and atorvastatin). Despite mandatory AE reporting requirements, FDA is aware that not all AEs associated with PAXLOVID were reported; therefore, the incidences of these events cannot be calculated based on these data.

Benefit-Risk Considerations

When considering the benefit versus risk of PAXLOVID in the context of the risk for serious adverse reactions due to DDIs, the benefit-risk assessment at the population level is different than the benefit-risk assessment for an individual patient. This is particularly relevant in the current stage of the pandemic when >90% of U.S. adults have received a COVID-19 vaccine and/or had a prior SARS-CoV-2 infection and when other treatment options are available. While PAXLOVID appears to reduce the risk of hospitalization and death by ~50 to 90% in all high-risk patients (i.e., the RRR), the absolute risk of hospitalization and death without treatment was ~2% in high-risk patients who had previously been vaccinated or had serologic evidence of baseline SARS-CoV-2 immunity in the PAXLOVID clinical trials (see Section 3.1.1.2).

This risk reduction in the COVID-19 vaccinated or SARS-CoV-2 seropositive high-risk population remains a large benefit on a population level. There were approximately 4000 COVID-19 related deaths and 35,000 COVID-19 related hospitalizations each week in the United States in January 2023 (CDC 2023a); consequently, even with a conservative estimate of benefit (25% of PAXLOVID-eligible patients unable to take PAXLOVID due to DDIs and an RRR of 50%), PAXLOVID could still lead to approximately 1500 lives saved and 13,000 hospitalizations averted each week in the United States.

However, on an individual patient level, with an absolute risk reduction with PAXLOVID for the hospitalization/death endpoint of about 1 to 2% for a patient with baseline SARS-CoV-2 immunity, individual patients could have DDIs associated with risks that could outweigh this benefit, particularly if the DDIs are not adequately managed. Whether or not the DDIs can be managed such that PAXLOVID would have a favorable benefit-risk assessment varies both by the specific medication and by the individual patient. Some of the medications that are either contraindicated or have a recommendation of "avoid concomitant use" with PAXLOVID cannot be safely held (either because the DDI risk would not be mitigated by holding the medication because of that medication's PK parameters, such as an extended half-life, or because the medication is needed to manage a serious medical condition), such that PAXLOVID would not be an appropriate choice. For other medications, the DDIs could be managed by temporarily holding the medication (e.g., atorvastatin), adjusting the dose of the concomitant medication, close laboratory monitoring, and/or monitoring for AEs. In addition, prescribers should also consider patient factors, such as a patient's ability to comply with instructions for dose adjustment or monitoring, the patient's estimated risk for development of severe COVID-19, and

[13] Drugs included in the August 25, 2022, update to the PAXLOVID Fact Sheet for Healthcare Providers, plus verapamil (added in the February 1, 2023 update) were used to determine drugs with PAXLOVID DDIs.

the patient's risk from the particular adverse reaction associated with the DDI, when deciding whether to prescribe PAXLOVID to their individual patient with risk of DDIs.

Risk Mitigation Strategies

Further risk mitigation through addition to PAXLOVID labeling of a boxed warning conveying the risk of serious adverse reactions due to PAXLOVID DDIs was discussed amongst the PAXLOVID review team and at a February 15, 2023, meeting with the FDA Center for Drug Evaluation and Research (CDER) Medical Policy and Program Review Council (MPPRC). A boxed warning could help to highlight the risk of serious adverse reactions due to PAXLOVID DDIs and better ensure that the potential for DDIs is considered by all prescribers, both to determine if actions are needed to manage the DDIs, and also to determine whether PAXLOVID is appropriate for that particular patient.

The following three situations in which Boxed Warnings can be used, per the FDA Guidance for Industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format* , apply to the risk of serious adverse reactions due to PAXLOVID DDIs (October 2011):

1. There is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug.
   - Some of the PAXLOVID DDIs are potentially life-threatening, and the absolute risk reduction of hospitalization/death with PAXLOVID in the overall high-risk population in 2023, when most adults have some baseline SARS-CoV-2 immunity from vaccination or prior infection, is estimated to be about one to two percent. Consequently, it is essential to consider DDIs when assessing the risks and benefit of using PAXLOVID.
2. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection and avoiding certain concomitant therapy).
   - Adverse reactions from PAXLOVID DDIs can be prevented or reduced in frequency or severity by adjusting or avoiding certain concomitant medications, by increased monitoring, or by selecting patients who are not taking medications with DDIs that could result in serious adverse reactions.
3. To highlight warning information that is especially important to the prescriber.
   - PAXLOVID is prescribed by a very broad group of healthcare providers, many of whom may not be familiar with ritonavir and its drug interactions. In addition, PAXLOVID is often prescribed in an urgent care setting where prescribers may not be familiar with the patient and their concomitant medications. Consequently, it is especially important that the risk of DDIs be highlighted to prescribers.

The Applicant's main rationale against adding the boxed warning is that a boxed warning may lead to prescriber hesitancy. They state that claims data suggested addition of a boxed warning reduced prescriptions by 12% to 75% for Premarin, Febuxostat, Celebrex, and Chantix. However, the examples provided were for boxed warnings about serious risks that could apply to all patients taking the drug and involved drugs that are indicated for smoking cessation or symptomatic relief of a non-life-threatening condition for which other products are available. The proposed boxed warning for PAXLOVID would only apply to patients taking medications

with clinically significant DDIs, and PAXLOVID is a product that reduces the risk of COVID-19 related hospitalization and death. Furthermore, a boxed warning would presumably only decrease PAXLOVID prescriptions for patients on medications with DDIs that would make PAXLOVID use inappropriate or for patients being seen by prescribers unwilling or unable to manage DDIs, situations in which the risk would outweigh the benefit for the individual patient.

The following points were discussed at the MPPRC meeting, and the MPPRC unanimously agreed with the review team's proposal to include a boxed warning to communicate the risk of serious adverse reactions due to DDIs in PAXLOVID labeling.

Conclusion

Serious adverse reactions due to DDIs are the key safety concern with PAXLOVID. Safety surveillance data under EUA indicate that many PAXLOVID-eligible patients are on medications with DDIs with PAXLOVID (though the most common medications with DDIs could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring), that the majority of PAXLOVID prescribers are adult primary care practitioners (who may not be experienced in managing ritonavir DDIs), and that serious adverse reactions, including death, have been reported in association with DDIs that are included in the EUA FS for HCP despite previous risk mitigation efforts. For these reasons, and with supportive advice from the CDER MPPRC, the USPI will include a boxed warning to highlight this important safety risk. The specific drugs included in the USPI as having clinically significant drug interactions with PAXLOVID, along with recommended actions, will be carried over from the most recent PAXLOVID EUA FS for HCP with a few updates (see Section 8.2.2).

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Age, Weight, Gender, and Race

The population PK model included data from 1237 subjects, including 150 subjects from Phase 1 studies and 1087 subjects from EPIC-HR. Age ranged from 18 to 86 years and baseline BMI ranged from 16.6 to 58.1 kg/m^2. Of the 1237 subjects, 657 (52.6%) were male, 580 (46.4%) were female, 865 (69.2%) were white, 105 (8.40%) were black, 162 (13.0%) were Asian, 95 (7.60%) were American Indian/Alaska Native and 10 (0.8%) were other or unknown. Gender and race were not significant covariates on nirmatrelvir PK. While age was a significant covariate on central volume of distribution, the approximately 25% reduction for subjects aged 80 years or above is not considered to be clinically relevant (See Section 14.5).

Exposure of nirmatrelvir was lower in a subset of four Japanese subjects enrolled in the multiple-dose PK and safety study, Study 1001, (AUC_{tau} and C_{max} approximately 30% and 21% to 26% lower) compared to non-Japanese subjects. These numeric differences in exposures are unlikely to be clinically meaningful. Mean half-life, drug accumulation and urinary recovery of unchanged nirmatrelvir were comparable between the two groups (see Section 14.2).

8.1.2. Renal Impairment

The primary route of elimination of nirmatrelvir when administered with ritonavir is renal excretion of intact drug. A dedicated renal impairment study (Study 1011) enrolled subjects with mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min) or severe (eGFR <30 mL/min and not requiring dialysis) renal impairment and a control group of subjects with normal (eGFR ≥90 mL/min) renal function. Subjects received 100 mg nirmatrelvir on 0 hours on Day 1 and 100 mg ritonavir on Day 1 and at -12 hours, 0 hours,12 hours, and 24 hours in relation to the Day 1 nirmatrelvir dose. Urinary recovery of unchanged nirmatrelvir was 31%, 43%, 31%, and 18% for the normal, mild impairment, moderate impairment, and severe impairment renal groups, respectively. Mean AUC_{inf} values of nirmatrelvir in subjects with mild (eGFR 60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe renal impairment (eGFR <30 mL/min) were 1.24 (0.99, 1.54), 1.87 (1.49, 2.36) and 3.04 (2.38, 3.90), respectively (see Section 14.2).

No dose adjustment is recommended in patients with mild renal impairment (eGFR 60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min) the recommended dose is 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days.

Study 1011 noted a higher incidence of AEs in patients with severe renal impairment (see Section 14.2). Given the mean 204% increase in AUC_{inf} and anticipated higher exposures at the clinical nirmatrelvir dose of 300 mg twice daily (co-administered with ritonavir 100 mg twice daily), PAXLOVID is not recommended in patients with severe renal impairment until more data are available. A safety and PK study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis) is ongoing, Study C4671028; NCT05487040, and will provide additional data to inform the appropriate dose for patients with severe renal impairment; therefore, this trial is a recommended postmarketing requirement (PMR) inclusion in the Approval Letter.

8.1.3. Hepatic Impairment

Hepatic elimination is not expected to be a major route of elimination for nirmatrelvir in combination with ritonavir based on Phase 1 data. In Study 1001, the only drug-related entity in plasma was unchanged nirmatrelvir. A dedicated hepatic impairment study (Study 1010) enrolled subjects with moderate (Child-Pugh Class B) hepatic impairment receiving a single dose of nirmatrelvir 100 mg and 4 doses of ritonavir 100 mg at -12 hours, 0 hours, 12 hours, and 24 hours. The exposure of nirmatrelvir in moderate hepatic impairment subjects was comparable to those in subjects with normal hepatic function. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment to normal hepatic function were 0.99 (0.71, 1.38) and 1.02 (0.74, 1.40), respectively (See Section 14).

No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No PK or safety data are available regarding the use of nirmatrelvir or ritonavir in patients with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment.

8.2. Extrinsic Factors

8.2.1. Food Effect

A dedicated food effect study (Study 1019) evaluated the effect of a high-fat meal (fat is 50% of total caloric content of the meal containing 800 to 1000 calories) on the relative bioavailability of the commercial 150 mg nirmatrelvir tablet boosted with 100 mg ritonavir. When taken orally with a high-fat meal versus fasted, the $AUC_{0-\infty}$ and C_{max} (geometric mean ratio [90% CI] of nirmatrelvir were 1.20 (1.09, 1.32) and 1.61 (1.39, 1.86).

All subjects in EPIC-HR (conducted using the to-be-marketed formulation of nirmatrelvir, co-administered with ritonavir) and the supportive Phase 2/3 trials were dosed without regard to food based on results from the first-in-human Study 1001 which showed co-administration of a high-fat meal with the boosted nirmatrelvir suspension resulted in an increase in AUC and C_{max} of 1.5% and 15%, respectively.

PAXLOVID is recommended to be given without regard to food given the favorable efficacy and tolerable safety profile noted in EPIC-HR when dosed without regard to food.

8.2.2. Drug Interactions

8.2.2.1. Effects of Nirmatrelvir/Ritonavir on Other Drugs

The potential DDI liability of nirmatrelvir as a perpetrator (effect of nirmatrelvir on the PK of other drugs) is based on in vitro studies conducted using nirmatrelvir alone.

The inhibitory potency of nirmatrelvir was determined by measuring the activity of each cytochrome P450 (CYP) enzyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) in pooled human liver microsomes at a concentration range from 0.01 to 300 µM for all CYPs.

Nirmatrelvir reversibly and time-dependently inhibited CYP3A4 and did not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, CYP2B6 or CYP1A2 in vitro at clinically relevant concentrations (Table 47).

Table 47. Assessment of Risk for CYP Inhibition In Vitro Between Nirmatrelvir and Co-Administered Substrates

Basic (R1) Reversible Model		
CYP	**IC_{50} (µM)**	**R Value**
CYP1A2	>300	<1.02
CYP2B6	>300	<1.02
CYP2C8	>300	<1.02
CYP2C9	>300	<1.02
CYP2C19	>300	<1.02
CYP2D6	>300	<1.02
CYP2A4/5 Midazolam	58.3	1.09
CYP3A4/5 Testosterone	106	1.05
CYP3A4/5 Nifedipine	45.1	1.12

Basic (R1, gut) Reversible Model		
CYP	**IC50 (µM)**	**R Value**
CYP2A4/5 Midazolam	58.3	83.2
CYP3A4/5 Testosterone	106	46.3
CYP3A4/5 Nifedipine	45.1	107
Basic (R2) TDI Model		
CYP	**Ki,u (µM)**	**R Value**
CYP2A4/5 Midazolam	15.5	26.4
CYP3A4/5 Testosterone	13.9	30.8

Source: Study PF-07321332_04Nov20_113907, Study PF-07321332_09Nov20_122202.
Abbreviations: CYP, cytochrome P450; IC_{50}, half-maximal inhibitory concentration; R1, ratio of intrinsic clearance values of a probe substrate in the absence and in the presence of the interacting drug; R2, ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug for TDI; Ki, u, unbound dissociation constant; TDI, time-dependent inhibition.

The in vitro induction effect of nirmatrelvir on CYP3A4, CYP2B6, CYP1A2, CYP2C9 and CYP2C19 was evaluated in cultured human hepatocytes at nirmatrelvir concentrations of 0.01 to 200 µM. Nirmatrelvir exhibited less than a 2-fold induction of enzyme activity at clinically relevant concentrations in all hepatocytes evaluated.

In a mechanistic model, the predicted net effect of nirmatrelvir on CYP3A was inhibition with no inhibition noted for the other enzymes (Table 48).

Table 48. Mechanistic Model of CYP Mediated DDI Risk Assessment of Nirmatrelvir[a]

	Reversible Inhibition		TDI		Induction						
	Intestinal	Hepatic	Intestinal	Hepatic	Intestinal	Hepatic	AUC_{R1}	AUC_{R2}	AUC_{R3}	$AUC_{R1,2}$	$AUC_{R1,2,3}$
CYP	Ag (≤0.8)	Ah (≤0.8)	Bg (≤0.8)	Bh (≤0.8)	Cg (≥1.25)	Ch (≥1.25)	Rev	Tdi	Ind	Rev,tdi	Rev,tdi,ind
1A2	--	0.99	--	--	--	--	1.01	--	--	--	--
2B6	--	0.99	--	--	--	1.54	1.00	--	0.82	--	--
2C8	--	0.99	--	--	--	1.73	1.00	--	0.75	--	--
2C9	0.94	0.99	--	--	2.05	1.30	1.01	--	0.77	--	--
2C19	0.94	0.99	--	--	1.70	1.28	1.01	--	0.77	--	--
2D6	0.94	0.99	--	--	--	--	1.01	--	--	--	--
3A	0.46	0.82	0.04	0.10	8.76	3.74	1.56	11.87	0.06	13.83	4.36
3Ahepatic	1	0.82	1	0.10	1	3.74	1.20	7.11	0.28	8.14	2.86
3Aintestinal	0.46	1	0.04	1	8.76	1	1.29	1.67	0.23	1.70	1.53

Source: PF-07321332_04Nov20_113907, PF-07321332_09Nov20_122202, PF-07321332_18Oct20_102559.

[a.] The terms listed in the table have the following values:

- Ag = 1 / (1 + [I]g/Ki)
- Ah = 1 / (1 + [I]h/Ki)
- Bg = kdeg,g / (kdeg,g + [I]g•kinact/([I]g + KI))
- Bh = kdeg,h / (kdeg,h + [I]h•kinact/([I]h + KI))
- Cg = 1 + d•E_{max}•[I]g /([I]g + EC50)
- Ch = 1 + d•E_{max}•[I]h / ([I]h + EC50)
- AUCR = 1 / (Ag•Bg•Cg•(1 − fg) + fg) • 1 / (Ah•Bh•Ch•fm + (1 − fm))

Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; DDI, drug-drug interaction; ind, induction; rev, reversible; TDI, time-dependent inhibition.

In vitro transporter inhibition studies demonstrated that nirmatrelvir inhibits P-gp ([I]/IC50=34) and OATP1B1 (R1=1.11). In vitro inhibition was not observed for BCRP, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Ritonavir is a strong CYP3A4 inhibitor that is co-administered with nirmatrelvir to increase plasma nirmatrelvir concentrations. Ritonavir also inhibits P-gp and is a weak inhibitor of CYP2D6. Ritonavir also induces CYP3A (net effect is strong inhibition), CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

Clinical DDI studies were conducted by the applicant to evaluate the effect of nirmatrelvir/ritonavir on the PK of midazolam and dabigatran, a CYP3A substrate and P-gp substrate, respectively. The effects of nirmatrelvir/ritonavir on midazolam and dabigatran AUC and C_{max} are summarized in Table 49. Oral midazolam is contraindicated in the PAXLOVID labeling. Depending on dabigatran indication and patient's renal function, the PAXLOVID label recommends reducing the dose of dabigatran or to avoid concomitant use. There was no additional effect of nirmatrelvir on midazolam PK or dabigatran PK beyond that caused by ritonavir alone in either study (Section 14.2).

Table 49. Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Co-Administered Drug

Co-Administered Drug Dose (Schedule)	Nirmatrelvir/Ritonavir Dose (Schedule)	N	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	
			C_{max}	AUC[a]
Midazolam[b] 2 mg (1 dose)	300 mg/100 mg BID (9 doses)	10	3.68 (3.19, 4.25)	14.30 (12.04, 17.00)
Dabigatran[b] 75 mg (1 dose)	300 mg/100 mg BID (5 doses)	24	2.33 (1.72, 3.16)	1.94 (1.55, 2.44)

Source: Study 1012, Study 1013.
[a.] AUC = AUC_{inf} for both midazolam and dabigatran.
[b.] For midazolam, Test = nirmatrelvir/ritonavir plus midazolam, Reference= Midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test= nirmatrelvir/ritonavir plus dabigatran, Reference= Dabigatran. Dabigatran is an index substrate for P-gp.
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; CYP, cytochrome P450; N, number of subjects in group; P-gp, P-glycoprotein

In the clinical DDI study with midazolam, there was no incremental effect of nirmatrelvir on midazolam PK beyond that caused by ritonavir alone. Further, maximal CYP3A4 inhibition has been noted with ritonavir at doses of 50 mg to 100 mg and is used as a booster with HIV protease inhibitors at a dose of 100 mg once or twice daily (Mathias et al. 2009). Since the DDI potential of PAXLOVID is mainly associated with ritonavir component, with full CYP3A inhibition anticipated at the clinical dose, the list of contraindicated drugs and clinically significant drug interactions generally aligns with the Norvir (ritonavir) and boosted protease inhibitor USPIs. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC when co-administered with ritonavir. Thus, co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

Drugs That Are Contraindicated With PAXLOVID

The review team recommended deletion of (b) (4) from the list of contraindicated drugs in the PAXLOVID label. The inclusion of this drug was originally proposed by the Applicant (b) (4)

(b) (4)

The PAXLOVID label includes a clinical comment in Table 1 recommending careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression when narcotic analgesics are concomitantly administered with PAXLOVID).

Like rifampin, rifapentine is also a strong CYP3A inducer. The review team reclassified rifapentine as a drug that is contraindicated with PAXLOVID based on the risk of significantly reduced nirmatrelvir or ritonavir plasma concentrations that may be associated with the potential for loss of virologic response and possible resistance.

In addition, the following drugs were added to the list of drugs that are contraindicated with PAXLOVID based on their inclusion in the NIH guidelines for DDIs with PAXLOVID, the concomitant drug label, or the Norvir or boosted protease inhibitor labeling: silodisin, eplerenone, ivabradine, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primodine, and lumacaftor/ivacaftor.

Drugs That Should be Avoided With PAXLOVID

Drug interaction recommendations in the PAXLOVID label are generally aligned with recommendations outlined in ritonavir-containing drug labels. In addition, the following drugs are added based on their inclusion in the NIH guidelines for DDIs with PAXLOVID or post-authorization safety reports suggestive of a significant interaction: tamsulosin,aliskiren, ticagrelor, vorapaxar, clopidogrel, ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, everolimus, rimegepant, hydrocodone, oxycodone, suvorexant, tadalafil, avanafil, vardenafil, and sildenafil when used for erectile dysfunction (already included when used for pulmonary arterial hypertension).

Drugs That Require a Dose Adjustment or Additional Monitoring When Co-Administered With PAXLOVID

Similarly, the following drugs are added based on their inclusion in the NIH guidelines for DDIs with PAXLOVID or post-marketing safety reports suggestive of a significant interaction.

Language added in the PAXLOVID label is consistent with the concomitant drug label and the Norvir or boosted protease inhibitor USPIs: disopyramide, apixaban, clonazepam, cilostazol, saxagliptin, tofacitinib, upadacitinib, darifenacin, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, riociguat, tadalafil and verapamil.

While other ritonavir-containing products are generally prescribed by HIV specialists experienced at managing the multiple drug interactions with ritonavir, PAXLOVID is being prescribed by a much broader group of healthcare providers. A boxed warning for DDIs has been added to the PAXLOVID labeling to further highlight this potential serious risk (See 7.7.1).

8.2.2.2. Effect of Other Drugs on Nirmatrelvir/Ritonavir

Clinical DDI studies were conducted with carbamazepine and itraconazole, a CYP3A inducer and CYP3A inhibitor, respectively. The effects of carbamazepine and itraconazole on nirmatrelvir/ritonavir AUC and C_{max} are summarized in Table 50. Co-administration of PAXLOVID with strong CYP3A inducers including carbamazepine is contraindicated due to potential loss of virologic response and possible resistance.

Based on the results of the itraconazole DDI study, no significant increase in nirmatrelvir exposure is expected with concomitant use of additional CYP3A inhibitors, including co-administration with additional boosting agents such as cobicistat or additional doses of ritonavir. The expected increase in nirmatrelvir exposure in this scenario is well below what was noted with the supratherapeutic nirmatrelvir dose (administered with ritonavir) that was well tolerated in Study 1001. Therefore, no dose adjustments are needed when PAXLOVID is given to patients who are also on a ritonavir- or cobicistat-containing regimen.

Table 50. Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-Administered Drugs

Co-Administered Drug Dose (Schedule)	Nirmatrelvir/Ritonavir Dose (Schedule)	N	Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	
			C_{max}	AUC[a]
Carbamazepine[b] 300 mg BID(16 doses)	300 mg/100 mg BID (5 doses)	9	0.57 (0.47, 0.69)	0.45 (0.34, 0.59)
Itraconazole 200 mg QD (8 doses)	300 mg/100 mg BID (5 doses)	11	1.19 (1.13, 1.25)	1.39 (1.29, 1.49)

Source: Study 1014 and Study 1015.
[a.] For carbamazepine, AUC = AUC_{inf}, for itraconazole, AUC = AUC_{tau}.
[b.] Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; CYP, cytochrome P450; N, number of subjects in group; P-gp, P-glycoprotein; QD, once per day

The effect of moderate and weak CYP3A inducers on nirmatrelvir/ritonavir PK has not been studied in clinical DDI studies. There are several published clinical DDI reports with other ritonavir combinations (i.e., 100 mg-200 mg total daily dose) and the moderate CYP3A inducer, efavirenz. The effect of efavirenz on ritonavir PK when ritonavir was administered in combination with indinavir, darunavir, or nelfinavir is summarized in Table 51.

Table 51. Effect of Efavirenz (Moderate Inducer of CYP3A4) on PK of Ritonavir in Protease Inhibitor Combinations

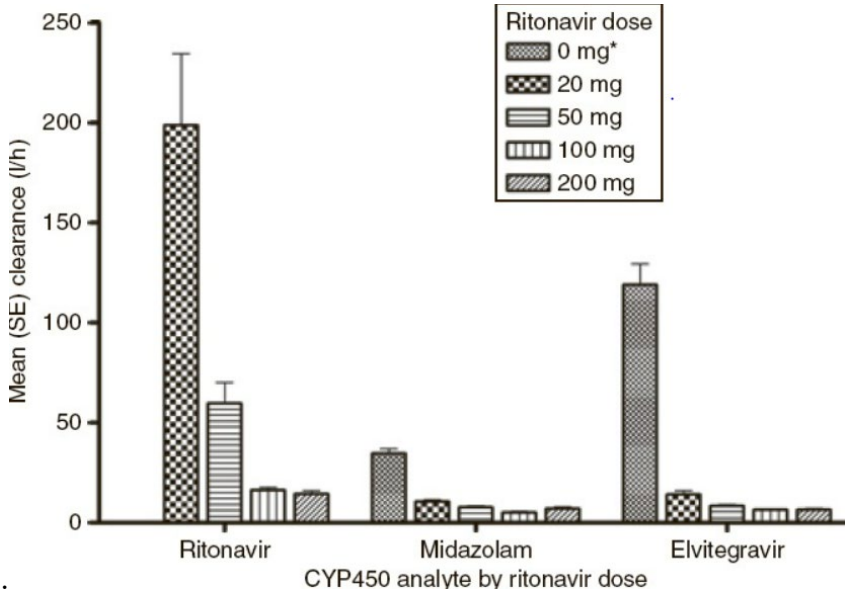
Dose/Regimen of Efavirenz	Dose/Regimen of Ritonavir	AUCR For Ritonavir	AUCR for Protease Inhibitor	Reference
600 mg QD Days 15-29	100 mg BID (in combination with 800 mg BID indinavir) Days 1-29	0.64	0.75	(Aarnoutse et al. 2002)
600 mg QD Days 10-24	100 mg, QD (in combination with 900 mg darunavir QD) Days 1-24	0.74	0.86	(Soon et al. 2010)
600 mg QD Days 11-20	200 mg, QD (in combination with 1875 mg nelfinavir) Days 1-20	0.80	1.30	(la Porte et al. 2004)

Source: Table generated from Reviewer analysis.
[a.] AUCR = AUC ratio = AUC of ritonavir or PI in presence of efavirenz/AUC of ritonavir or PI in absence of efavirenz.
Abbreviations: BID, 2 times per day; PI, protease inhibitor; QD, once per day

The ritonavir dose-response relationship on CYP3A metabolism using the HIV integrase inhibitor elvitegravir and the CYP3A substrate midazolam was evaluated by Mathias et al (Mathias et al. 2009). In this study, the effect of increasing doses of ritonavir on CYP3A activity was assessed by changes in midazolam and elvitegravir clearance (through inclusion of historical CL from an earlier study of elvitegravir administered without ritonavir). The lowest dose of ritonavir tested resulted in substantial reduction (approximately three- and ninefold, respectively) in midazolam clearance and elvitegravir oral clearance. Further increases in the ritonavir dose resulted in more modest additional reductions in midazolam and elvitegravir clearance, indicating that maximum ritonavir-mediated inhibition of CYP3A-mediated metabolism is achieved at ritonavir doses of 50 to 100 mg (Figure 18).

Based on the data provided by Mathias et al, this decrease in ritonavir exposure produced by moderate CYP3A inducer such as efavirenz, and by extension weak CYP3A inducers, is unlikely to affect the ability of ritonavir to inhibit CYP3A (Mathias et al. 2009).

Figure 18. Ritonavir, Midazolam, and Elvitegravir Clearance Values (Mean [SE]) by Ritonavir Dose



Source: (Mathias et al. 2009).
Note: The asterisk represents historical data for elvitegravir.
Abbreviations: CYP, cytochrome P450; SE, standard error

To further investigate the potential effects of moderate CYP3A inducers on ritonavir and ritonavir-boosted drugs, the PBPK reviewer collected and analyzed publicly available data of clinical DDI studies of moderate CYP3A inducers with ritonavir-boosted antiviral products and showed that the maximal reduction in the AUC of ritonavir was 63%. In most cases, lesser reduction was observed in AUCs of the corresponding boosted drugs. The trough concentrations (C_{min}) of the boosted drugs, which are often the more relevant PK parameter to the efficacy of these antivirals, were more vulnerable to the induction than their AUCs. Whether a moderate CYP3A inducer reduces the C_{min} of the boosted drugs may depend on the dose of each co-administered component, the combination of co-administered components, and drug interaction potentials of the boosted drugs. Therefore, it is difficult to estimate the effects of moderate CYP3A inducers on the exposure of ritonavir-boosted nirmatrelvir solely based on these available clinical DDI data. PBPK simulations need to be performed for this purpose. Assuming ritonavir AUC was reduced up to 63% by moderate CYP3A inducers, moderate CYP3A inducers were predicted to have little effects on nirmatrelvir PK by using a ritonavir PBPK model modified by the reviewer and the nirmatrelvir model developed by the Applicant. Based on this result, little changes are expected for weak CYP3A inducers.

Additional Drug Interaction Considerations

Patients on Concomitant Contraindicated HMG-CoA Reductase Inhibitors

Due to the potential for myopathy including rhabdomyolysis, lovastatin and simvastatin are both contraindicated with concomitant use of PAXLOVID. However, forgoing an efficacious outpatient treatment of COVID-19 may have a greater clinical consequence than pausing the concomitant use of simvastatin or lovastatin for a 5-day treatment duration. Given simvastatin and lovastatin are taken in the evening and have a short half-life, a clinical comment was added to labeling to include a timeframe in which patients on simvastatin or lovastatin are eligible for

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PAXLOVID therapy. Specifically, patients should discontinue lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.

Instructions were also added to hold these statins during the five days of PAXLOVID treatment and for five days after completing PAXLOVID.

The recommendation to hold the statin for five days after completion of PAXLOVID is based on the estimated time course of CYP3A recovery after removal of enzyme inhibition. In the publication by Stader et al, a modeling approach was used to evaluate the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir (Stader et al. 2020). lopinavir/ritonavir (400/100mg twice daily) was administered for 7 days in a virtual trial to achieve steady state CYP3A inhibition and the abundance of CYP3A was estimated for 21 consecutive days. The interaction potential after stopping lopinavir/ritonavir was investigated with midazolam (a CYP3A probe substrate) administered orally 5 mg once-daily starting on the seventh day. In all simulations conducted, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/ritonavir. While complete disappearance of CYP3A inhibition took 21 days, the amount of inhibition remaining at five days is not expected to be clinically significant for most drugs.

In another publication by Hong et al, a PBPK simulation-based approach was applied to predict the effect of ritonavir on the PK of elexacaftor-tezacaftor-ivacaftor (ETI) and determine a potential dose alteration of ETI to overcome the CYP3A inhibition mediated by ritonavir (Hong et al. 2022). Steady-state PK of standard dose ETI alone and when co-administered with 100 mg ritonavir twice daily for 5 days were simulated. A dose reduction of ETI during 5 days of ritonavir administration with resumption of full dose of ETI on day 9 (4 days after stopping ritonavir) provided a similar steady-state PK profile of the conventional regimen of ETI alone. Based on the totality of available information, a recommendation to hold lovastatin or simvastatin during the five days of PAXLOVID treatment and for five days after completing PAXLOVID was included in the prescribing information of PAXLOVID.

Patients on Hormonal Contraceptives

Patients on hormonal contraceptives are instructed to consider an additional, non-hormonal method of contraception during the five days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID. This recommendation is based on the theoretical risk of reduced ethinyl estradiol exposure with ritonavir and is supported by data from the darunavir/ritonavir package insert and a study by Kasserra et al, demonstrating a significant decrease ethinyl estradiol exposure when co-administered with darunavir/ritonavir (600 mg/100 mg) for 14 days or 100 mg ritonavir for 10 days, respectively (Janssen Products 2011; Kasserra et al. 2011). While the involvement of CYP enzymes are likely a minor contributor to this interaction, the time course of the additional processes involved in ethinyl estradiol metabolism (including glucuronidation and sulfation) are not well characterized. Generally, contraceptive efficacy is attributed to progestin more than the estrogen component. However, loss of efficacy due to lower ethinyl estradiol exposure cannot be ruled out, since efficacy may be affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation, and endometrial lining changes.

Patients on Immunosuppressant Therapy

Concomitant use of a strong CYP3A inhibitor such as ritonavir can increase the risk of toxicities associated with immunosuppressants that have a narrow therapeutic index (e.g., cyclosporine, tacrolimus and sirolimus). Therapeutic concentration monitoring is recommended for patients on these drugs, although the frequency varies and decreases once the patient is on stable treatment. Therefore, language was added in the PAXLOVID label to avoid concomitant use of PAXLOVID in patients who are unable to undergo close monitoring of cyclosporine or tacrolimus serum concentrations. Concomitant use of sirolimus and a strong CYP3A inhibitor is not recommended even with the option of therapeutic concentration monitoring, consistent with the sirolimus labeling.

8.3. Plans for Pediatric Drug Development

The NDA for PAXLOVID triggers Pediatric Research Equity Act (PREA) as a new active ingredient. In their agreed initial Pediatric Study Plan, (b) (4) Their ongoing trial includes all pediatric patients, including neonates.

EPIC-PEDS is an ongoing open-label, multicenter, single-arm pediatric study to evaluate the safety, pharmacokinetics, and efficacy of PAXLOVID in non-hospitalized, symptomatic pediatric patients who are at risk of progression to severe disease. The following age cohorts will be evaluated:

- Cohort 1: weight ≥40 kgs, 6 to <18 years (b) (4)
- Cohort 2: weight ≥20 to < 40 kg, 6 to <18 years (b) (4)
- Cohort 3: ≥2 to <6 years (b) (4)
- Cohort 4: ≥1 month to <2 years (b) (4)
- Cohort 5: birth to <1 month (b) (4)

PAXLOVID will be supplied as the commercial tablet formulation in Cohort 1 and 2 and as an (b) (4) formulation [supplied as (b) (4)] in Cohorts 3 to 4; and in Cohort 2 for subjects who are unable to be administered tablets.

(b) (4)

Division of Antivirals (DAV) met with Pediatric Review Committee (PeRC) on March 7, 2023. The PeRC agreed with the deferral request in pediatric subjects from birth to less than 18 years of age, including neonates, with mild to moderate COVID-19. To collect safety and PK data in the pediatric population and to help determine the appropriate PAXLOVID dose in specific age

and weight brackets, the following Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) are recommended for inclusion in the Approval Letter:

1. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects 6 to less than 18 years of age and weighing 20 kg or higher, with mild-to-moderate COVID-19
2. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects 2 to less than 6 years of age, with mild-to-moderate COVID-19
3. Conduct a study to evaluate the safety, tolerability, PK, and treatment response of PAXLOVID in pediatric subjects from birth to less than 2 years of age with mild-to-moderate COVID-19

(b) (4)



8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Nonclinical Data

The developmental and reproductive toxicology studies with nirmatrelvir and ritonavir are summarized in Section 7.1.

Nirmatrelvir

There were no effects on fertility or reproductive performance in rats exposed to nirmatrelvir at exposures approximately 5 times higher than clinical exposure at the recommended human dose (RHD) of PAXLOVID.

In a rat embryo-fetal developmental study, no biologically significant developmental effects were noted at exposure 10 times higher than clinical exposure at the RHD of PAXLOVID. In the rabbit embryo-fetal developmental study, lower fetal body weights (9% decrease) were observed at approximately 13 times higher than clinical exposure at the RHD of PAXLOVID. No

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developmental effects were observed in rabbits at exposures approximately 4 times higher than clinical exposures at the RHD of PAXLOVID.

In a rat pre- and postnatal developmental (PPND) study, a transient, non-adverse decrease (less than 8%) in the body weight of offspring was observed. Nirmatrelvir exposure was not assessed in the plasma of nursing pups or in the milk of lactating animals. However, it is estimated that no developmental effects occur in pregnant rats at approximately 6 times higher than clinical exposure at the RHD of PAXLOVID.

Ritonavir

No fertility effects were noted in rats administered ritonavir at 18 and 26 times (in males and females, respectively) higher than clinical exposure at the RHD of PAXLOVID.

At a maternally toxic exposure approximately 10 times higher than clinical exposure at the RHD of PAXLOVID, increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the clinical exposure at the RHD of PAXLOVID. No evidence of teratogenicity was observed in rats and rabbits.

In a rat PPND study, exposure of ritonavir at 3 times higher than clinical exposure, based on a body surface area conversion factor, resulted no developmental effects.

Clinical Data

Across the PAXLOVID clinical trials, there have been seven cases of maternal exposure during pregnancy. In four cases, female subjects received placebo. In the remaining three cases, the pregnancies occurred in female partners of male subjects receiving PAXLOVID and the outcome of the pregnancies in these cases was unknown as of December 31, 2022. In all three cases there were no associated AEs. No female subjects who received PAXLOVID reported a pregnancy.

In a cumulative search of postmarketing AE reports for cases reporting pregnancy or lactation through December 31, 2022, the Applicant identified a total of 101 cases of exposure during pregnancy and 14 cases involving lactation.

Of the 101 cases of exposure during pregnancy, trimester of exposure was unknown in 22 cases. In 13 cases, exposure occurred during the first trimester of pregnancy. In 35 cases, exposure occurred during the second trimester and in 31 cases, exposure occurred in the third trimester of pregnancy. Infant outcome was reported in eight cases: normal in four babies, one baby was born prematurely at 29+1 weeks and was hospitalized in the neonatal ICU due to prematurity of birth (no abnormalities reported). In one case, spontaneous abortion was reported four days after the end of PAXLOVID. One case reported neonatal respiratory failure and congenital abnormalities of brachial cyst and anal fistula in an infant exposed during the seventh month of pregnancy.

A total of 14 cases involved lactation: suppressed lactation in 3 cases, lactation disorder in one case, and exposure via breastmilk in 10 cases.

The OSE also evaluated cases from the FAERS database, Pfizer's Monthly Safety Reports, the ACMT – FDA ACMT COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Sub-registry, and the published literature for AE and medical errors. Through August 29, 2022, 11 cases of pregnancy were identified. Two cases reported AEs: one case with preterm

premature rupture of membranes and one case reported spontaneous abortion. There were two cases reporting signs/symptoms consistent with hypersensitivity reaction: one case reported angioedema and skin erythema and one case reported shortness of breath, wheezing, hypoxia, lip and pharyngeal swelling, and pruritus. Four cases reported only COVID-19 rebound with no AEs. The remaining three cases reported AEs similar to those observed in all patients, with the majority being labeled in the PAXLOVID EUA FS for HCP (dysgeusia, diarrhea, nausea).

To collect safety outcome data in pregnant individuals and their infants after PAXLOVID use during pregnancy, to help inform PAXLOVID dosing recommendations during pregnancy, and to inform use of PAXLOVID during lactation, the following PMCs pertaining to ongoing or planned studies are recommended for inclusion in the Approval Letter:

- An observational study to evaluate pregnancy and infant outcomes following exposure to PAXLOVID during pregnancy
- A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Orally Administered PAXLOVID in Pregnant Women With Mild-to- Moderate COVID-19 (Study C4671035; NCT05386472)
- A Phase I, Multiple Dose, Open-Label Pharmacokinetic Study of PAXLOVID in Healthy Lactating Women (Study C4671039; NCT05441215)

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed NDA 217188 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective The drug product blisters contain immediate release tablets of nirmatrelvir, 150 mg and ritonavir,100 mg. The marketing of two dosage presentations is proposed - they differ only in having either one or two nirmatrelvir tablets in each dose pack. The blister packs have been updated since the EUA to contain single doses – instead of the daily dose packs in the EUA product. Nirmatrelvir tablets are manufactured by the Applicant whereas the ritonavir tablets are sourced from two previously approved sources - AbbVie (NDA 22417) and Hetero (ANDA 204587). The data provided support the quality and labeling of the proposed product including a (b) (4) retest period for nirmatrelvir and a 24-month expiry period for both nirmatrelvir tablets and ritonavir tablets. The PAXLOVID co-packaged drug product expiry date will reflect the shorter expiry of the two components.

Three Comparability Protocols were found acceptable (b) (4) - all CBE-30 supplements. Pfizer committed to submit CBE-0 supplement with the three-month long-term and accelerated stability data for three nirmatrelvir tablets batches manufactured at (b) (4) site by July 2023. Pfizer also committed to submit additional supporting assay data for the environmental assessment as a CBE-0 submission by December 2023.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Due to data reliability issues detailed in Section 6.3.1, certain sites in EPIC-HR, EPIC-SR, and EPIC-PEP were excluded from the final analyses. After excluding these sites, the result of the clinical site inspections and Applicant inspection support the conclusion that the clinical trials were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 6.3.1 for a summary of inspection findings and Section 25 for financial disclosures.

11. Advisory Committee Summary

The Antimicrobial Drugs Advisory Committee (AMDAC) met on March 16, 2023 to discuss this NDA. Please refer to the AMDAC meeting web page for full details (FDA 2023). Below are the questions posed to the AMDAC followed by a summary of the discussion.

1. VOTE: Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?

a. If yes, please provide your rationale.

b. If no, please provide your rationale and list what additional studies/trials are needed

Vote Result: Yes: 16 No: 1 Abstain: 0

Committee Discussion: A majority (94%) of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The committee members acknowledged that it will be important to identify who is still at high risk for progression to severe disease in the current setting when most people have some baseline SARS-CoV-2 immunity to understand who is most likely to benefit from PAXLOVID. Several committee members commented that since the absolute magnitude of benefit from PAXLOVID has decreased since the trials were conducted due to increasing levels of baseline SARS-CoV-2 immunity from vaccination or prior infection, the risks of treatment (mainly the drug-drug interactions) will have greater weight when making a benefit-risk assessment for use of PAXLOVID in an individual patient. There was also discussion about the continued emergence of new SARS-CoV-2 variants, and the committee

indicated the importance of having an antiviral product like PAXLOVID available, considering that it has retained activity against variants to date and, given the conserved nature of the Mpro drug target, is predicted to retain activity against future variants. Committee members also stated that the absence of other oral, easy-to-administer, effective alternative therapies are also favorable factors when considering the benefit-risk assessment for PAXLOVID. Several committee members commented that it will be important to communicate that PAXLOVID will have the greatest benefit if taken early after symptom onset, specifically within 5 days as was studied in the trials. When it came to safety, drug-drug interactions were an area of significant concern, and many agreed that this is an issue that needs to be addressed further. There was discussion that risk mitigation is needed in terms of better communicating the risk of drug-drug interactions as primary care providers are primarily prescribing PAXLOVID and may not be familiar with ritonavir drug-drug interactions. Completion of studies pertaining to pregnancy, pediatrics, and in the immunocompromised population was emphasized. The committee member who voted "No" was concerned that the community does not understand where PAXLOVID fits in, who will benefit, and therefore who will be able to access and use it in a timely and appropriate way. Please see the transcript for details of the committee discussion.

2. DISCUSSION: Please comment on the strength of evidence for use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations:

a. Individuals who are vaccinated against COVID-19 or had prior SARS-CoV-2 infection

b. Individuals infected with Omicron subvariants

c. Individuals who are immunocompromised

Please comment if additional data are needed in these populations.

Committee Discussion: Committee members agreed that a patient-level benefit-risk assessment, i.e., clinical judgement or personalized medicine, will be needed for the use of PAXLOVID, but more data are needed to guide physicians in understanding who meets the risk criteria and who will benefit in the right population. Members of the committee also stated that having systematic data on which populations are still at high risk for progression to severe disease in the current era of high population immunity will allow physicians to be more informed, as the issue is not whether there is benefit, but rather in which patients the magnitude of benefit of PAXLOVID will outweigh the risks. The committee agreed that ongoing surveillance and research should be conducted to ensure that emerging Omicron subvariants and other future variants continue to be susceptible to PAXLOVID and to detect the possible emergence of resistant variants. The committee recommended that pharmacovigilance plans and nonclinical studies should be implemented to study PAXLOVID activity against new emerging variants. Concerning the immunocompromised population, committee members stated that the clinical development plan for investigating use of PAXLOVID in immunocompromised patients, including the clinical trial EPIC-IC, seems to be comprehensive. However, there was concern that with the wide spectrum of immunocompromising conditions, one study may be insufficient to fully inform decision making with this population. Several committee members commented that collection of samples to look for prolonged viral shedding and emergence of resistant virus would be important in EPIC-IC. Please see the transcript for details of the committee discussion.

3. DISCUSSION: Please comment on the strength of evidence for an association between use of PAXLOVID in the treatment of mild-to-moderate COVID-19 and 'COVID-19 rebound'. Please comment if additional data are needed.

Committee Discussion: Regarding COVID-19 rebound, many of the committee members highlighted that the clinical trial data clearly show that COVID-19 rebound occurred in both the placebo and PAXLOVID groups and that PAXLOVID use was not the driving factor for COVID-19 rebound. Committee members also commented that they are seeing reassuring data in the published literature, and that as healthcare professionals it is essential to effectively convey the information. Multiple committee members noted that the main issue is that the perception that PAXLOVID causes COVID-19 rebound persists, even among the medical community, although this is not supported by data but rather perpetuated by anecdotal reports and confirmation bias. Members emphasized the importance of communicating information based on the science and data and putting it into context so that those who would benefit from treatment are not turned away due to a concern that is not fully understood. Please see the transcript for details of the committee discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the ACT), the Secretary of the Department of Health and Human Services determined that there is a public health emergency that has a significant potential to affect national security or the health and security of the United States citizens living abroad, and that involves the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19). On November 25, 2020, Pfizer, Inc. (Pfizer) submitted a pre-investigational new drug (IND) meeting request to obtain Agency feedback on the regulatory and data requirements necessary to rapidly advance development of PF-07321332 as a potential oral treatment of SARS-CoV-2. The Agency provided detailed written feedback on the overall clinical and non-clinical drug development program for initial IND submission on January 13, 2021.

Pfizer submitted IND 153517 for the treatment of COVID-19 on December 22, 2020. Upon review of the IND application, on January 25, 2021, the IND was placed on full clinical hold due to insufficient information to assess risk to human subjects due to the absence of a clinical protocol, insufficient CMC information, lack of investigators' information, and lack of an investigator's brochure. Pfizer submitted a complete response to the clinical hold letter on February 3, 2021, and the Agency removed clinical hold on February 23, 2021.

On May 12, 2021, a meeting request was submitted to obtain Agency's feedback on the type of clinical and nonclinical information that would be needed to support an emergency use authorization (EUA) and full new drug application (NDA) submission for PF-07321332. The Agency's written responses dated May 27, 2021, provided feedback on the Pfizer's plan for the product packaging presentation; proposed nonclinical safety strategy and planned clinical/clinical pharmacology programs to support a future NDA submission; and additional clinical and virology (regarding assessment of antiviral activity of the product). In addition to the planned studies, the Agency recommended conducting drug-drug interaction studies to assess the effect of strong inducers and strong inhibitors of CYP3A4 on the pharmacokinetic (PK) of PF-07321332 and also recommended to initiate the hepatic impairment study. In addition, the Agency provided additional guidance for a future submission of an EUA application for the treatment and pre-exposure of symptomatic COVID-19.

Pfizer submitted the initial Pediatric Study Plan (iPSP) for PF-07321332/ritonavir (b) (4)

[redacted] (b) (4). The final agreed iPSP contains the following:

1. [redacted] (b) (4)
2. Deferral of assessment in the pediatric population from [redacted] (b) (4) to less than 18 years of age with a planned study start of 1Q2022 for adolescents (12 to less than 18 years of age who weigh 40kg or more)

The Agreed Initial Pediatric Study Plan (iPSP) was issued on April 4, 2022.

On August 10 and August 13, 2021, Pfizer requested a waiver from conducting a thorough QT/QTc study and the removal of the requirements for continued electrocardiogram (ECG) monitoring in the phase 2/3 clinical trials (EPIC-SR (C4671002), EPIC-HR (C4671005), and EPIC-PEP (C4671006)) based on preliminary ECG analysis from Part 5 of C4671001, ECG data from the sentinel cohort in trial C4671005 (EPIC-HR) and External Data Monitoring Committee recommendation which found no evidence of a cardiac safety signal. The Agency agreed with the assessment and recommendation to discontinue ECG monitoring in the phase 2/3 trials. In reference to the QT/QTc trial proposal, Pfizer follow up with a subsequent submission dated December 20, 2021 with a proposal to potentially rerun the good laboratory practice (GLP) hERG study in a format that aligns with the ICH S7B guidance currently in development. The Agency notified that the Applicant's strategy to use an integrated clinical (Study #C4671001) and double-negative nonclinical assessment
(hERG study 211129.QHJ and in vivo QT study 20GR275) to support the QT assessment under ICH E14 Q&A 5.1 appeared reasonable.

On November 3, 2021, the proposed proprietary name, PAXLOVID, was found acceptable and the proprietary name was conditionally granted.

Based on the clinical development program conducted under IND 153517 and in pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), on October 21, 2021, initial Emergency Use Authorization (EUA) request was submitted for treatment of mild-to-moderate COVID-19. Shortly after, Pfizer submitted nonclinical and CMC information to support the EUA application. On December 22, 2021, the Agency issued an EUA for PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighting at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death based on the totality of scientific evidence available to the Agency, including data from the clinical trial EPIC-HR, a phase 2/3 randomized, double blind, placebo-controlled clinical trial.

On January 28, 2022, Fast Track Designation Request was submitted for treatment of COVID-19 and the request was granted on February 17, 2022, which allowed the following:

1. Interactions with the Agency to discuss the drug's development plan to support a marketing application
2. The eligibility for priority review if supported by clinical data at the time of marketing application submission
3. The ability for the Agency to consider reviewing portions of the marketing application before the complete submission is received by the Agency

On February 15, 2022, a Type B Meeting Request was submitted to obtain the Agency's advice regarding the submission of a New Drug Application (NDA) for the use of Paxlovid in the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death. The Written Response was issued on April 13, 2022 providing feedback on the structure, format, and data plan for future NDA submission including:

1. Sufficiency of nonclinical toxicology safety studies
2. Nonclinical antiviral resistance assessments
3. Planned integration of safety data (EPIC-HR and EPIC-SR) from PAXLOVID clinical trials and proposed format, standards, and structure of the datasets to be submitted
4. Viral sequencing reports
5. Format and criteria of safety narratives

The Agency recommended to clarify the "Indication/Claims" that will be submitted at the time of original NDA submission and re-iterated that a major amendment to an unapproved NDA may not include data to support an indication or claim that was not included in the original NDA submission, but it may include data to support a minor modification of the indication or claim that was included in the original NDA submission. The Agency agreed with the nonclinical safety studies conducted to support an NDA submission and reminded Pfizer of additional final study report timelines for outstanding animal studies.

The Agency did not fully agree with the proposed nonclinical virology antiviral resistance studies to support the NDA submission and requested the mouse hepatitis virus (MHV) selection study report PF-07321332_12Oct21_035634 be included in the NDA submission as this study could still be supportive for identifying potentially important nirmatrelvir resistance pathways. Based on breakthrough cases observed in EPIC-HR, the Agency recommended Pfizer continue to phenotypically characterize specific amino acids changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical and clinical studies and include a current data with cumulative data from these studies in the NDA submission.

The Agency did not agree with the totality of data proposed to support an NDA submission and recommended to include EPIC-PEP and/or EPIC-SR efficacy data with the original NDA submission.

On May 9, 2022, a Type B, preNDA CMC-only Meeting Request was submitted to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 105 to NDA 217188 and to receive feedback on CMC specific questions in preparation for NDA submission. The preliminary comments were sent to the Pfizer on May 20, 2022, and during teleconference held on May 24, 2022, between Pfizer and Office of Pharmaceutical Quality (OPQ), OPQ provided feedback on the CMC information for future NDA submission including:

1. Additional product (DS and DP) manufacturing facilities
2. Plan to align CMC content between NDA and EUA
3. Period of stability data plan
4. Dissolution specification method

The Agency recommended Pfizer to submit all changes that will impact commercial supply to the NDA. The Agency was unable to comment on (b) (4) [redacted]. Generally, the Agency expects that at least 12 months of long-term stability data and 6 months of accelerated stability data for three primary drug product batches be included in the initial NDA submission per the recommendations in ICH Q1A(R2). However, for a product being developed to address an unmet medical need, the Agency agreed to accept less stability data for the primary batches in the initial NDA submission. The Agency agreed with Pfizer's proposal to submit 9-month stability data at the time of NDA submission and 12-month stability data in mid-September. The Office of Pharmaceutical Quality offered regular meetings with the Applicant during NDA review to discuss CMC issues.

On June 29, 2022, Pfizer submitted an original NDA 217188 for PAXLOVID, 300/150mg tablet to support the following indication: "PAXLOVID which includes nirmatrelvir, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor, and ritonavir, an human immunodeficiency virus (HIV-1) protease inhibitor and CYP3A inhibitor, is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death."

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Selected nonclinical studies were originally submitted and reviewed under IND 153517 and EUA 105. All nonclinical safety studies conducted in support of PAXLOVID were also submitted to the present NDA 217188 and are reviewed in the following sections. Data supporting ritonavir were reviewed previously under NDA 20659 and are not summarized in this section.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Pharmacology

13.2.1.1. Secondary Pharmacology

In vitro studies suggest nirmatrelvir has minimal potential for secondary (off-target) pharmacology at clinically relevant concentrations. The in vitro off-target pharmacology of nirmatrelvir was assessed at 100 µM in a broad target profiling panel representing targets with known links to potential safety concerns and includes G-protein coupled receptors, ion channels,

transporters, and enzymes. No activity greater than 50% was observed. The IC_{50} values for nirmatrelvir inhibition of the Nav1.5 (peak) sodium and the Cav1.2 calcium channel currents were both determined to be >300µM, the highest concentration tested. Inhibitory activity of PF-07321332 against 11 phosphodiesterase (PDE) subtypes (1 to 11) and the IC_{50} values were determined to be >200µM (the highest concentration tested) for all tested PDE subtypes.

13.2.1.2. Safety Pharmacology

Table 52. Safety Pharmacology Studies

Study Title/Study No.	Findings
Effects of PF-07321332-00 on Cloned *hERG* Potassium Channels (Study# 22LJ022) • In vitro study, PF-07321332 at 30 and 300 µM was tested	The *hERG* inhibition of PF-07321332 at 300 µM was statistically significant ($p < 0.05$), but the *hERG* inhibition of PF-07321332 at 30 µM was not statistically significant ($p > 0.05$) when compared to vehicle control values. when compared with the vehicle control group. The IC50 for the inhibitory effect of PF-07321332 on *hERG* potassium current was not calculated but was greater than 300 µM.
Effects of PF-07321332 on Cardiac Function and Condition on the Guinea Pig Isolated Langendorff-Perfused Heart Model (Study# 20LJ075) • Ex vivo study	There were no statistically significant ($p<0.05$) effects on cardiac contractility, left ventricular pressure, coronary perfusion pressure, and the PR, QRS or QT intervals at any of the concentrations tested (0.03 µM-100 µM).
Assessment of the Effects of PF-07321332 on the Rat Isolated Aorta Preparation (Study# 20LJ076) • Ex vivo study on aorta cultured in buffer	PF-07321332 (2 pM - 100 µM) did not produce a vasoconstriction response in the rat isolated aorta tissue bath preparation (EC50 value >100 µM).
Safety Pharm-Cardiovascular Assessment of Oral Gavage PF-07321332 in Conscious Telemetry Instrumented Male Cynomolgus MONKEYS (Study# 20GR275) • Male cynomolgus monkeys, 0, 40 (20 BID), and 150 (75 BID) mg/kg • Single dose	PF-07321332 at 40 (20 BID) mg/kg/day produced no test article-related effects. PF-07321332 at 150 (75 BID) mg/kg/day increased systolic, diastolic, and mean blood pressures. Additionally, PF-07321332 decreased heart rate and LV +dP/dt max (an indicator of contractility) as well as increased RR-, PR- and QT-intervals. PF-07321332 at 150 (75 BID) mg/kg/day also produced a decrease in QTc-interval. All measures returned to vehicle control levels within 24 HPD.

Study Title/Study No.	Findings
PF-07321332: Neurofunctional and Pulmonary Assessment in Male Wistar Han Rats Following Oral (Gavage) Administration (Study# 20GR274) • Male rats (6/group) • 0, 60, and 1000 mg/kg, single dose	• In the quantitative locomotor assessment, a single, oral administration of 1000 mg/kg PF-07321332 resulted in test article-related higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30-minute period compared with vehicle control. Administration of 1000 mg/kg PF-07321332 also produced drug-related lower number of mean vertical movement counts (-36%) during the first 5-minute period of the quantitative locomotor assessment compared with vehicle control. There were no test article-related effects on any FOB parameters following oral administration of PF-07321332 up to 1000 mg/kg. • In the pulmonary assessment, administration of 1000 mg/kg PF-07321332 resulted in a test article-related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle control from 40 to 160 minutes post dose during a 6-hour continuous monitoring period.

Source: Reviewer assessment.
Abbreviations: BID, twice a day; EC50, half-maximal effective concentration; hERG, human ether-a-go-go-related gene; HPD, hours postdose; IC50, half-maximal inh bitory concentration; PR, period from P wave to the start of the QRS complex; QRS, end of PR interval to the end of S wave; QTc, QT interval corrected for heart rate; RR, cycle length variability and interval between successive Rs; QT, interval from beginning of QRS complex to the end of the T wave

13.2.2. Absorption, Distribution, Metabolism, Excretion/PK

13.2.2.1. Absorption

Single IV or oral dose absorption studies were conducted in Wistar-Han rats (PF-07321332_24Nov20_103131) and Cynomolgus monkeys (PF-07321332_19Nov20_111728). In the rat study, two oral formulations were tested, (b) (4) form of nirmatrelvir (10 or 100 mg/kg) and (b) (4) form (10, 100, 300, 1000 mg/kg). In both species, plasma CL was moderate, with a moderate to low V_{ss}, and $t_{1/2}$ values were 5 hours in rats and <1 hour in monkeys after IV dosing (Table 53). Following oral dosing, the overall bioavailability was moderate to high (29 to >100%) in rats but low (<10%) in monkeys.

Table 53. Pharmacokinetics of Nirmatrelvir in Rats and Monkeys

Dose[a] (mg/kg)	Route	N	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	%F
Rat (PF-07321332_24Nov20_103131)									
1	IV	2	27.2	1.8	5.1	--	--	632	--
10	PO	2	--	--	4.0	1.5	1290	3190	50
10[b]	PO	3	--	--	2.8	0.25	1450	2170	34
100	PO	2	--	--	14[c]	0.75	29100	58600[c]	>100
100[b]	PO	3	--	--	5.7	1.4	5300	18100	29
300	PO	2	--	--	NR[d]	0.38	48900	153000	81
1000	PO	2	--	--	8.7	1.0	88300	750000	>100
Monkey (PF-07321332_19Nov20_111728)									
1	IV	2	17.1	0.33	0.8	--	--	977	--
10	PO	2	--	--	NR[d]	0.25	1450	NR[e]	8.5

Source: Applicant's Pharmacokinetics written summary, Section 2.6.4.3. Table 2.6.4-1.
[a.] All forms of nirmatrelvir were from the (b) (4) lot of material unless noted otherwise.
[b.] The (b) (4) form of nirmatrelvir was dosed.
[c.] N = 1.
[d.] Parameter not reported due to lack of discernible elimination phase.
[e.] Parameter was not reported due to increase in concentration at the last timepoint.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CL, apparent clearance; C_{max}, maximum plasma concentration; %F, bioavailability; IV, intravenous; N, number of subjects in analysis; PO, per os (by mouth); $T_{1/2}$, half-life; T_{max} time it takes for the drug to reach maximum concentration; V_{ss}, apparent volume of distribution at steady-state

Toxicokinetic data of nirmatrelvir were evaluated from the GLP repeat dose oral toxicity studies in rats and monkeys. Please see Section 13.2.3.2 for detailed information.

13.2.2.2. Distribution

In Vitro

- Protein binding was evaluated in plasma from rats, human and monkey (07321332_23Nov20_010657). The binding of nirmatrelvir to plasma proteins in rat, monkey, and human was moderate and similar across concentrations and species. Plasma protein binding was also evaluated in rabbits and dogs and concentration-dependent binding was observed (Study PF-07321332_23Nov20_020334; YDP/067/394, Table 54).
- Preliminary data indicates that nirmatrelvir primarily binds to Alpha-1-acid glycoprotein (AAG).
- At a concentration of 1µM, nirmatrelvir preferentially partitioned into plasma relative to red blood cells with Cb/Cp ratios of 0.83 (rat), 0.68 (monkey), and 0.60 (human) (Study PF-07321332_18Nov20_100444).

Table 54. Plasma Protein Binding of Nirmatrelvir

Species (Strain)	0.3 µM[a]	1 µM[a]	Plasma 3 µM[a]	Fu 10 µM[a]	Average[b]
Rat (Wistar Han)	0.490	0.474	0.484	0.467	0.479
Monkey (Cynomolgus)	0.386	0.404	0.449	0.499	0.435
Human	0.296	0.300	0.311	0.333	0.310

Species (Strain)	2 µM	10 µM	Plasma 30 µM	Fu[a] 50 µM	100 µM	200 µM
Rabbit (New Zealand White)	0.0100	0.449	0.734	0.737	0.817	0.804
Dog (Beagle)	0.0235	0.0977	0.404	0.542	0.640	0.685

Source: Modified based on Applicant's Pharmacokinetics written summary, Section 2.6.4.4. Table 2.6.4-4.
[a.] Geometric mean (n = 12).
[b.] Average value across the 4 concentrations tested.
Abbreviations: Fu, unbound drug

In Vivo

- The tissue distribution of [14C]nirmatrelvir was studied using Quantitative Whole Body Autoradiography (QWBA) in male Long-Evans rats (Study 8476949). Following administration of a single oral dose (1000 mg/kg, 160 µCi/kg) of [14C]nirmatrelvir, the distribution of radioactivity was widespread by 0.5 hours. The majority of tissues (except for liver, intestines, and kidneys) had tissue:plasma AUC_t ratios <1.0. The tissues with the highest C_{max} values (T_{max} = 4 hours for most tissues) excluding the gastrointestinal tract were observed in the liver, kidney, pancreas, and adrenal gland. [14C]nirmatrelvir-derived radioactivity did not cross the blood:brain barrier to a quantifiable extent. These results are consistent with nirmatrelvir being a substrate for P-gp. In most tissues, the elimination of [14C]nirmatrelvir-derived radioactivity was complete by 24 hours. [14C]nirmatrelvir did not associate with melanin-containing tissues.

13.2.2.3. Metabolism

In Vitro

- The metabolic profile of nirmatrelvir was evaluated in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human) (Study PF-07321332_09Nov20_084546).
  - A total of five oxidative metabolites were detected in vitro. The primary metabolite was M4 (PF-07329268), which arose from a mono-hydroxylation at the C-5 position of the pyrrolidinone ring, yielding a pair of interconverting diastereomers. The other sites of oxidation resulted in the formation of minor metabolites.
  - All oxidative metabolites were formed by CYP3A4/5, with other cytochrome P450 (CYP) enzymes contributing very minor amounts.
- The formation of M5 was observed in incubations of nirmatrelvir in human gut microbiota (Study PF-07321332_12Oct21_082057), alongside the destrifluoroacetyl metabolite M8 (PF-07331782). Approximately, 3.1% and 1.4% of nirmatrelvir was converted to M5 and M8 over the course of a 24-hour incubation with gut microbiota.
  - Hydrolysis was not observed in human-derived in vitro systems including human whole blood, intestinal fluid, and S9 fractions from liver, kidney, intestine, and lung.

- In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was the major contributor (fm = 0.99) to the oxidative metabolism of nirmatrelvir. No significant CYP3A5 contribution is expected to the metabolism of nirmatrelvir (Study PF07321332_21Nov20_072016).
- Reaction phenotyping studies were conducted in human liver microsomes to identify the UGT enzymes responsible for the in vitro glucuronidation of M5 (PF-07320267). Results indicated UGT2B4 and 2B7 contributed 69.8% and 16.7% of the total metabolism of M5, respectively. The remaining 13.5% of metabolism through the UGT pathway was unassigned (Study PF-07321332_11Aug21_021055).

In Vivo

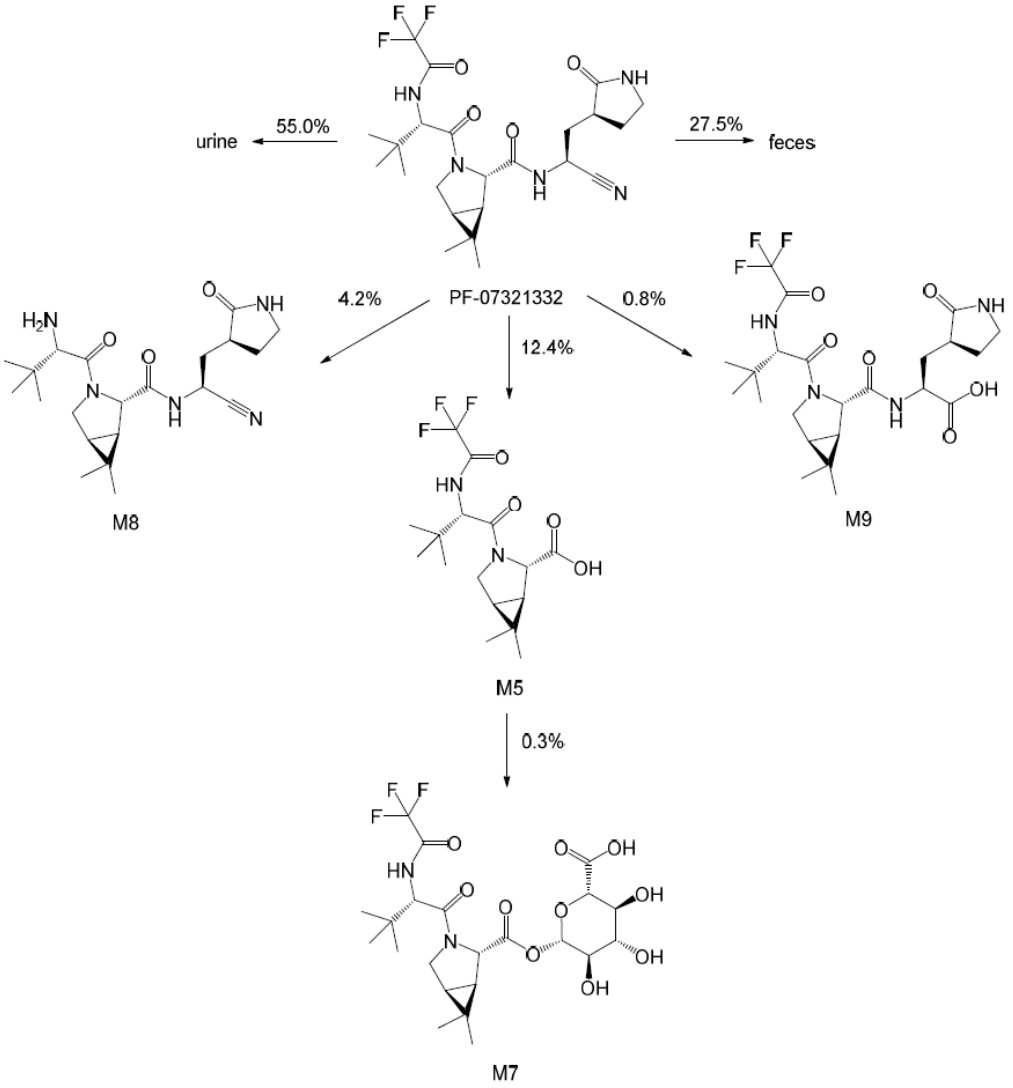
- The metabolism of nirmatrelvir was evaluated in vivo in rat and monkey after repeat oral dosing (Study PF-07321332_09Nov20_084546).
  - Besides oxidative biotransformation pathways, metabolite M5 (PF-07320267) obtained through hydrolytic cleavage across an amide bond in nirmatrelvir, was also detected as a minor metabolite in circulation and excreta from animals.
- M5 was also detected in circulation (trace levels) and excreta in humans when nirmatrelvir was co-administered with ritonavir.
- No unique human circulatory metabolites were detected.

13.2.2.4. Excretion

- Urinary and/or biliary excretion of nirmatrelvir was assessed in single-dose PK studies after IV or oral dosing of nirmatrelvir to rats (Study PF-07321332_24Nov20_103131) and monkeys (Study PF-07321332_19Nov20_111728). The percentage of nirmatrelvir dose excreted unchanged was 17% in the urine, 9% in the bile, and up to 11% in the feces in rats, and 7% in the urine and 4% in the feces in monkeys.
- The mass balance excretory pathways and metabolic profile of unlabeled nirmatrelvir was evaluated in six healthy subjects (C4671001, Cohort 9) following a single dose of 300 mg, co-administered with 100 mg ritonavir (Study PF-07321332_25Aug21_014401, Study PF-07321332_14Sep21_021626).
  - Unchanged nirmatrelvir represented 82.5% of the recovered dose in urine and feces at 55% and 28%, respectively.
  - Metabolite M5 (PF-07320267), arising via hydrolysis, was present at 12.1% of recovered dose almost exclusively in feces.
  - Metabolite M8 (PF-07331782) represented 4.2% of the recovered dose in urine and feces combined,
  - All other fluorine-containing metabolites were relatively minor (<1% of dose).
- The proposed metabolic pathways in humans are presented in Figure 19.

Reference ID: 5179402

Figure 19. Profile of Nirmatrelvir Metabolism and Disposition in Human Excreta Following Oral Co-Administration of 300 mg Nirmatrelvir With Ritonavir



Source: Applicant's Pharmacokinetic written summary. Section 2.6.4.6. Fig 2.6.4-2.
Abbreviations: M, metabolite

13.2.3. General Toxicology

13.2.3.1. Single-Dose Toxicology/Toxicokinetics

Single IV or oral dose absorption studies were conducted in Wistar-Han rats (PF-07321332_24Nov20_103131) and Cynomolgus monkeys (PF-07321332_19Nov20_111728) for pharmacokinetic parameters. Please see Section 13.2.2.1 for details.

13.2.3.2. Repeat-Dose Toxicology/Toxicokinetics

13.2.3.2.1. Two-Week Oral Gavage Toxicity and Micronucleus Assessment Study of PF-07321332 in Wistar Han Rats With a Two-Week Recovery (Study# 20GR276)

Key Study Findings

- Hematological, liver, and thyroid effects were observed.
- All of the hematology and coagulation findings (i.e., increase in prothrombin time (PT), APTT, PLT and FIB, decrease in RBC mass) had no clinical or microscopic correlations and all findings were completely resolved at the end of the recovery phase. Mechanisms for the increases in PT and APTT are unclear.
- The liver (i.e., minimal to mild periportal hepatocyte hypertrophy and vacuolation) and thyroid gland (i.e., thyroid follicular cell hypertrophy) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone clearance in the liver, a mechanism that rats are known to be particularly sensitive to, relative to humans. All of the findings observed in the liver and thyroid were low severity and the absence of associated microscopic evidence of tissue damage or correlating alterations in clinical pathology parameters, and all of these findings fully resolved after the 2-week recovery period.
- The no observed adverse effect level (NOAEL) is the high dose of 1000 mg/kg.
  - Exposure on study Day14 (male and female combined): AUC_{24} was 292,000 ng·h/mL and C_{max} was 51500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 4.3× based on human exposures

Table 55. Two-Week Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 200, and 1000 mg/kg/day; given once daily for 4 weeks.
Route of administration	Oral gavage
Formulation/vehicle	Suspension / Control 1: (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water; Control 2 (Vehicle): (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	10/sex/group (toxicity main study) 5/sex/group (toxicity recovery study/ 5/sex/control (TK) 5/sex/group (TK)
Age	9 weeks

Study Features and Methods	Details
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GLP, good laboratory practices; (b) (4); TK, toxicokinetic

Table 56. Two-Week Rat Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain and distress. No treatment-related deaths.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the days of necropsy. No treatment-related findings.
Body weights	All animals were weighed twice prior to the initiation of dosing on PID Days 1 and 7, predose on Dosing Phase Days 1, 8, 14, and a fasted weight was collected just prior to scheduled necropsy. During the recovery phase, body weights were collected on Recovery Phase Days 1, 8, and 11. There were no effects on body weight parameters in males. There was an increase (1.04x-1.12x mean controls) in body weight in females that was considered non-adverse due to magnitude.
Ophthalmoscopy	Ophthalmic examinations were performed on all animals once prior to the initiation of dosing on PID Days 4/5 (males/females) and on Toxicity animals on Dosing Phase Day 14. No treatment-related findings.
Hematology	Blood samples were collected from animals on the day of necropsy. There were dose-dependent prolongations in PT in males at ≥60 mg/kg/day (16-15%), and at 1000 mg/kg/day in females (40%), prolongations in APTT in males at ≥200 mg/kg/day (9-19%) and at 1000 mg/kg/day in females (11%) with no clinical or microscopic correlates. The mechanism for the increases in PT and APTT is unclear but indicates alterations in the coagulation pathway. Platelets were higher at 1000 mg/kg/day in both sexes (22-25%). In females only, there were lower RBC mass parameters (HGB, HCT, RBC) as indicated by HGB (5%) and higher fibrinogen (10%) at 1000 mg/kg/day. All hematology and coagulation findings recovered at the end of recovery phase.
Clinical chemistry	Drug-related clinical chemistry findings at 1000 mg/kg/day included higher globulin in both sexes (7%), and higher cholesterol (33%), lower ALP (34%) and albumin/globulin ratio (10%) in females. The increases in platelets, fibrinogen, globulin and decrease in AG are suggestive of an underlying inflammatory process but lacked any microscopic correlates. All drug-related clinical chemistry findings recovered at the end of the recovery phase.
Urinalysis	Urine samples were collected from animals on the day of necropsy. Drug-related urinalysis findings at 1000 mg/kg/day included lower pH (10%) in males on Day 15 compared with the control group. All test article-related urinalysis findings recovered at the end of the recovery phase.
Gross pathology	Drug-related macroscopic findings occurred in the liver (abnormal size, enlarged) at 1000 mg/kg/day in males (1/10) and females (1/10). These findings were fully recovered at the end of the recovery phase.

Parameter	Major Findings
Organ weights	Higher mean absolute (Male 36%, female 59%) and relative (Male 35%, Female 54%) liver weights were observed in males and females at 1000 mg/kg/day. A correlating microscopic finding of periportal hepatocyte hypertrophy was observed in males and females at this dose. Lower mean absolute and relative heart weights (15%) were observed only in females at 1000 mg/kg/day. There were no microscopic correlates in the heart. In the recovery phase, there were no drug-related organ weight differences in the liver and heart in males and/or females.
Histopathology Adequate battery: Yes	Liver Minimal to mild periportal hepatocellular hypertrophy was noted in females at ≥200 mg/kg/day and in males at 1000 mg/kg/day. It was characterized by slight enlargement of hepatocytes with abundant homogeneous eosinophilic cytoplasm and sinusoidal compression. Periportal hepatocellular hypertrophy was associated with increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at 1000 mg/kg/day. Hepatocellular hypertrophy corresponded to higher mean liver weights in males and females and macroscopic liver finding of abnormal size (enlarged) in 1 male and 1 female at 1000 mg/kg/day. At the end of the recovery phase, microscopic changes had completely recovered as there were no drug-related microscopic findings in the liver at ≥200 mg/kg/day. Thyroid Gland Follicular cell hypertrophy was noted in males and females (minimal to mild) at 1000 mg/kg/day and was characterized by increased size and height of follicular cells. At the end of the recovery phase, microscopic changes had completely recovered as there were no drug-related microscopic findings in thyroid gland at 1000 mg/kg/day. Kidney Increased incidence and severity of hyaline droplet in the tubular epithelium was observed in the cortex of males administered vehicle containing (b) (4) or PF-07321332 compared with control males administered vehicle only. The incidence and severity (up to moderate) of this finding was generally comparable between (b) (4) control and 1000 mg/kg/day groups and was less (up to mild) in the 60 and 200 mg/kg/day groups, indicating that this finding was (b) (4) concentration-dependent. At the end of the recovery phase, the hyaline droplets in the kidney were noted in all (b) (4) administered animals but with lower incidence and/or severity and was comparable with vehicle controls indicating complete recovery of this finding.
Special evaluation: Micronucleus assessment	Blood was collected on day 4. Lower mean percent reticulocytes at 1000 mg/kg/day in males was noted, suggesting drug-related effect on erythrocyte production and maturation in males. However, the mean %reticulocyte values fell within the negative historical control range and are considered non-biologically relevant. There was no drug-related higher mean micronucleate reticulocytes in males and females. The oral administration of PF-07321332 did not induce micronuclei in the reticulocytes from peripheral blood of male and female rats.

Parameter	Major Findings
Toxicokinetics Sample collection times: days 1 and 25 at 0.5, 1, 2, 4, and 24 hours postdose.	**Table 57. Toxicokinetic Parameters in Male and Female (Combined) Rats**

Dose (mg/kg)	Day	C_{max} (µg/mL)	AUC_{24} (µg•h/mL)
60	1	12.9	27.3
	14	13.3	17.2
200	1	37.0	291
	14	27.1	80.5
1000	1	62.1	796
	14	51.5	292

Source: Text Table 1 from the toxicology study report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration

Source: Reviewer assessment.
Abbreviations: AG, albumin/globulin ratio; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; HCT, hematocrit; HGB, hemoglobin; (b) (4); PID, prior to initiation of dosing; PT, prothrombin time; RBC, red blood cell

13.2.3.2.2. Fifteen-Day Twice Daily (BID) Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys (Study# 20GR289)

Key Study Findings

- Nirmatrelvir-related findings in repeated oral dosing in monkeys for 15 days limited to emesis and increase in fibrinogen (FIB). Increased FIB maybe attributed to an inflammatory state but lacked a microscopic correlate.
- The NOAEL was 600 mg/kg based on the absence of adverse PF-07321332-related findings.

  Exposure on study Day 15 (male and female combined): AUC_{24} was 1220,000 ng·h/mL and C_{max} was 106000 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 17.8x based on human exposures.

Table 58. Fifteen-Day Monkey Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 40 (20 BID), 100 (50 BID), 600 (300 BID) mg/kg/day; once daily for 15 days.
Route of administration	Oral gavage
Formulation/vehicle	Suspension / Control 1: (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water; Control 2 (Vehicle): (b) (4) Polysorbate 80 in 0.5% (w/v) of methylcellulose A4M in purified water.
Species/strain	Monkey/Cynomolgus
Number/sex/group	3/sex/group
Age	3-5 years old
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: BID, twice daily; CT, Connecticut; GLP, good laboratory practices; (b) (4); USA, United States of America

Table 59. Fifteen-Day Monkey Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined once daily. No mortality or moribundity.
Clinical signs	Clinical signs were monitored once daily. Drug-related emesis was observed at 600 (300 BID) mg/kg/day in male and ≥100 mg/kg/day in female cynomolgus monkeys. The emesis was generally described as food-like material or clear/foamy liquid and observed approximately 1 hour after the 2nd daily dose or following the overnight period. In both vehicle and (b) (4) control groups, there was single incidence of emesis observed in 1 of 3 males and females each.
Body weights	All animals were weighed twice prior to the initiation of dosing on PID Days 1 and 9, predose on Day 1 and weekly thereafter, and a fasted weight was collected just prior to scheduled necropsy. Drug-related decrease in body weight at 600 (300 BID) mg/kg/day on Day 15 in 1 male Animal (Male 13) (0.91x Day 1).
Ophthalmoscopy	Ophthalmic examinations were performed once prior to the initiation of dosing on PID Days 7/8 (male/female), and on Dosing Phase Day 10. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals on PID Day 5/6 and Day 16. Drug-related increase in fibrinogen (72 -109%), compared with baseline, was observed in 2 males and 1 female administered 600 (300 BID) mg/kg/day.
Clinical chemistry	Blood samples were collected from fasted animals on PID day 5/6 and day 16. Decreases in sodium (4%) and chloride (7%), compared with baseline, were observed in a single animal administered 600 (300 BID) mg/kg/day.
Urinalysis	Urine was collected on day 16. Lower pH (20-27%) in males and females administered 600 (300 BID) mg/kg/day was noted.
Gross pathology	Animals were sacrificed on day 16. No treatment-related findings.
Organ weights	No drug-related organ weight change.
Histopathology Adequate battery: Yes	No drug-related microscopic changes.
Special evaluation: ECG	ECGs were collected once prior to the initiation of dosing (baseline) on PID Days 2/3 (males/females) and predose and approximately 1 hour after the first daily dose on Dosing Phase Day 13 on all animals. No treatment-related changes were noted.

Parameter	Major Findings
Toxicokinetics Sample collection times: days 1 and 15. 0.5, 1, 2, 4, 6 (prior to PM dose), 7, and 24 hours after the AM dose administration	**Table 60. Fifteen-Day Toxicokinetic Parameters in Monkey With Oral Administration**

Dose (mg/kg/day)[a, b]	Day	Sex	C_{max} (µg/mL)	AUC_{24} (µg•h/mL)
40 (20 BID)	1	Male	1.72	6.14
		Female	1.86	14.7
		Overall	1.79	10.4
	15	Male	2.65	8.79
		Female	2.18	10.4
		Overall	2.42	9.61
100 (50 BID)	1	Male	6.80	39.7
		Female	15.8	129
		Overall	11.3	84.2
	15	Male	7.91	33.1
		Female	15.6	72.1
		Overall	11.8	52.6
600 (300 BID)	1	Male	65.6	795
		Female	53.5	651
		Overall	59.6	723
	15	Male	121	1390
		Female	90.4	1060
		Overall	106	1220

Source: Table from the Applicant's toxicology report.
[a.] Animals were dosed orally twice daily for 15 days.
[b.] 3 animals/sex/dose group.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration

Source: Reviewer assessment.
Abbreviations: BID, twice daily; ECG, electrocardiogram; [redacted] (b) (4); PID, prior to initiation of dosing

13.2.3.2.3. One-Month Oral Gavage Toxicity Study of PF-07321332 In Wistar Han Rats with A Two-Week Recovery (Study# 21GR122)

Key Study Findings

- Dose-dependent higher platelets and prolongation in PT were observed at ≥200 mg/kg/day. There were no clinical nor anatomic pathology correlates for these findings.
- In the liver, periportal hepatocellular hypertrophy and vacuolation in males and females at ≥200 mg/kg/day were noted and were associated with higher mean liver weights and macroscopic findings at 1000 mg/kg/day. In the thyroid gland, follicular cell hypertrophy was noted in males and/or females at ≥60 mg/kg/day. In the pituitary gland, cytoplasmic vacuolation was noted in the endocrine cells of the pars anterior (males only) at ≥60 mg/kg/day. At the end of the recovery phase, the changes were completely resolved at all doses in females and at 60 and 200 mg/kg/day in males; partial resolution was observed in recovery males at 1000 mg/kg/day. These findings are likely a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation. This mechanism is usually considered to have little to no relevance to humans.
- The NOAEL was 1000 mg/kg/day.
  - Exposure on study Day 25 (male and female combined): AUC_{24} was 548,000 ng·h/mL and C_{max} was 44500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 7.9x based on human exposures.

Table 61. One-Month Rat Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 200, and 1000 mg/kg/day; one dose each day
Route of administration	Oral gavage
Formulation/vehicle	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	15/sex/group (toxicity, 10 for main study, 5 for recovery study) 5/sex/group (TK)
Age	8 weeks
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GLP, good laboratory practices; TK, toxicokinetic; USA, United States of America

Table 62. One-Month Rat Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain or distress. No drug-related death was noted.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the day(s) of necropsy. Sporadic salivation (all doses) and soft feces (200 and 1000 mg/kg/day) observed during the dosing phase.
Body weights	All animals were weighed twice prior to the initiation of dosing, predose on Dosing Phase Days 1, 8, 15, 22, and 28, and a fasted weight was collected just prior to scheduled necropsy. Body weights were collected on Recovery Phase Days 1, 8, 13 (females) and 14 (males). No drug-related wight difference was noted.
Feed consumption	Food intake was measured weekly. No treatment-related findings.
Ophthalmoscopy	Ophthalmic examinations were performed on all animals once prior to the initiation of dosing (PID Day 6) and on Dosing Phase Day 23. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals at terminal sacrifice Day 29 or Day 43/44. Dose-dependent higher platelets (1.12x-1.28x) were observed in males and females administered ≥200 mg/kg/day; in males administered ≥200 mg/kg/day and females administered 1000 mg/kg/day, this was accompanied by dose-dependent prolongations in PT (1.06x-1.15x). These findings lacked clinical and microscopic correlates.
Clinical chemistry	Blood samples were collected from fasted animals at terminal sacrifice Day 29 or Day 43/44. No treatment-related findings.
Urinalysis	Urine was collected prior to terminal sacrifice Day 29 or Day 43/44. No treatment-related findings.
Gross pathology	Enlargement and/or abnormal color (mottled) in females and 1 male at 1000 mg/kg/day. These were completely recovered at the end of the 2-week recovery phase.
Organ weights	Higher mean liver weights (1.07x-1.83x control) in males and females at ≥60 mg/kg/day were noted. Increase of liver weight was completely recovered at all doses in females and at 60 and 200 mg/kg/day in males. Higher liver weights (1.11x- 1.20x) was observed in recovery males at 1000 mg/kg/day.

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>• In the liver, minimal to mild periportal hepatocellular hypertrophy in males and females at ≥200 mg/kg/day with concomitant increased severity (mild) of periportal hepatocyte cytoplasmic vacuolation (females only) at 1000 mg/kg/day were noted.
• In the thyroid gland, minimal to mild follicular cell hypertrophy was noted in males and/or females at ≥60 mg/kg/day.
• In the pituitary gland, minimal to mild cytoplasmic vacuolation was noted in the endocrine cells of the pars anterior (males only) at ≥60 mg/kg/day.
• At the end of the recovery phase, the microscopic changes in the liver, thyroid gland, and/or pituitary gland (males only) were completely recovered at all doses in females and at 60 and 200 mg/kg/day in males; partial recovery (lower incidence and/or severity) of the microscopic findings in the liver, thyroid gland, and pituitary gland was observed in recovery males at 1000 mg/kg/day.
• The pattern of linked findings in the liver, thyroid and pituitary glands are consistent with a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation. This mechanism is usually considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans.</td></tr>
<tr><td>Special evaluation:
NA</td><td></td></tr>
<tr><td>Toxicokinetics
Sample collection times: days 1 and 25, and 0.5, 1, 2, 4, 24 hours postdose.</td><td>Table 63. Mean Overall (Male + Female) Toxicokinetic Parameters of PF-07321332 in Wistar Han Rat Plasma
<table>
<tr><th>Dose (mg/kg)</th><th>Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hours)</th><th>AUC_{24} (ng•h/mL)</th></tr>
<tr><td>60</td><td>1</td><td>16200</td><td>0.50</td><td>34800</td></tr>
<tr><td></td><td>25</td><td>12800</td><td>0.50</td><td>19200</td></tr>
<tr><td>200</td><td>1</td><td>35000</td><td>1.0</td><td>252000</td></tr>
<tr><td></td><td>25</td><td>26000</td><td>1.0</td><td>94900</td></tr>
<tr><td>1000</td><td>1</td><td>87300</td><td>2.0</td><td>982000</td></tr>
<tr><td></td><td>25</td><td>44500</td><td>1.0</td><td>548000</td></tr>
</table>
Source: Text Table 1 from the Applicant's toxicology study report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; T_{max}, time for drug to reach maximum concentration</td></tr>
</table>

Source: Reviewer assessment.
Abbreviations: PID, prior to initiation of dosing

13.2.3.2.4. One-Month BID Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys with a Two-Week Recovery (Study# 21GR125)

Key Study Findings

- Sporadic occurrences of emesis at 600 (300 BID) mg/kg/day were the only clinical observation.
- Increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) in males and a female at 600 (300 BID) mg/kg/day and increases in fibrinogen in males and

females at 600 (300 BID) mg/kg/day. Fibrinogen increases from baseline were also noted in controls, but the magnitude was slightly greater in nirmatrelvir treated animals. No nirmatrelvir-related changes in clinical pathology parameters were observed at the end of the recovery phase, although recovery couldn't be evaluated in males that had increased AST and ALT, as those animals were euthanized at the end of the dosing phase.

- The NOAEL was 600 mg/kg/day.
  - Exposure on study Day 28 (male and female combined): AUC_{24} was 991,000 ng·h/mL and C_{max} was 87500 ng/mL.
- The exposure margin, based on the lack of adverse effects, was 14x based on human exposures.

Table 64. Twenty-Eight-Day Monkey Oral Gavage Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) mg/kg/day, daily dosing
Route of administration	Oral gavage
Formulation/vehicle	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain	Rat/Wistar Hanover
Number/sex/group	Control and high dose: 5/sex/group (first three for main study, remaining two for recovery study) Low and mid doses: 3/sex/group
Age	3-3.5 years
Conducting laboratory	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results	None.

Source: Reviewer assessment.
Abbreviations: BID, twice daily; CT, Connecticut; GLP, good laboratory practices; USA, United States of America

Table 65. Twenty-Eight-Day Monkey Oral Gavage Toxicity Study Findings

Parameter	Major Findings
Mortality	On dosing days, 1 hour after the last animal dosed in the AM, before the 2nd daily dose, and 1 hour after the last animal dosed in the PM. Twice daily on recovery days. No mortality or moribundity in this study.
Clinical signs	Detailed clinical observations were performed once weekly at approximately the same time body weights were performed, and on the day(s) of necropsy. Sporadic occurrences of emesis (1-4 bouts) were observed in 9 of 10 monkeys at 600 (300 BID) mg/kg/day for at least 1-5 days during the dosing phase, beginning Day 1 through 23. In the vehicle control, 40 (20 BID), and 100 (50 BID) mg/kg/day group, there were isolated incidences of emesis (single bouts) observed in 2 of 5 males, 1 of 3 females, and 1 of 3 males, respectively. No other drug-related clinical signs are noted.
Body weights	Body weights were recorded weekly. A fasted weight was collected just prior to scheduled necropsy. No treatment related effects.
Feed consumption	Food intake was measured daily in the AM. No treatment related effects.
Ophthalmoscopy	Ophthalmic examination was performed once prior to the initiation of dosing on PID Days 10/11 (M/F), and on Dosing Phase Day 22. No treatment-related findings.

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Hematology</td><td>Blood samples were collected from fasted animals on PID day 2/3 (M/F), dosing phase day 29, recovery phase day 15/14 (M/F). Increases in fibrinogen (1.20x - 1.91x) in males and females at 600 (300 BID) mg/kg/day was noted. Fibrinogen increases from baseline were also noted in controls, but the magnitude was slightly greater in nirmatrelvir treated animals. No fibrinogen changes were noted at the recovery animals.</td></tr>
<tr><td>Clinical chemistry</td><td>Blood samples were collected from fasted animals on PID day 2/3 (M/F), dosing phase day 29, recovery phase day 15/14 (M/F). Increases in ALT (1.63x - 3.53x) and/or AST (2.68x - 7.41x) in males and a female at 600 (300 BID) mg/kg/day was noted. The recovery of ALT and AST was not determined.</td></tr>
<tr><td>Urinalysis</td><td>Urine was collected on day 29 and recovery phase day 15/14 (M/F). No treatment-related findings.</td></tr>
<tr><td>Gross pathology</td><td>Animals were sacrificed on days 29 and 45/44 (M/F). No treatment related findings.</td></tr>
<tr><td>Organ weights</td><td>No treatment-related effects.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>No treatment related findings.</td></tr>
<tr><td>Special evaluation:
ECG</td><td>ECG collection was performed prior to the initiation of dosing (baseline) on PID Days 4 (M) and 5 (F) and predose and 2 HPD (+/- 15 minutes) on Dosing Phase Days 24 (M) and 27 (F) on all animals. No drug-related changes in HR, RR-, PR-, QRS-, QT- or QTc-intervals for any of the comparisons described. There were no drug-related changes in ECG morphology.</td></tr>
<tr><td>Toxicokinetics
Sample collection times: On Day 1 and Day 28, 0.5, 1, 2, 4, 6 (prior to second daily dose), 7, and 24 hours after the first daily dose</td><td>Table 66. Mean Overall (M+F) Toxicokinetic Parameters ± Standard Deviation for PF-07321332 in Cynomolgus Monkey Plasma
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>Mean C_{max} (ng/mL)</th><th>Mean AUC_{24} (ng•h/mL)</th></tr>
<tr><td>40[a]</td><td>1</td><td>1250±584</td><td>4110±1340</td></tr>
<tr><td></td><td>28</td><td>1380±700</td><td>5620±1420</td></tr>
<tr><td>100[a]</td><td>1</td><td>5320±3060</td><td>29600±12100</td></tr>
<tr><td></td><td>28</td><td>7800±3440</td><td>45900±16800</td></tr>
<tr><td>600[b]</td><td>1</td><td>76600±21300</td><td>885000±239000</td></tr>
<tr><td></td><td>28</td><td>87500±21000</td><td>991000±227000</td></tr>
</table>
Source: Text Table 1 from the Applicant's toxicology study report.
[a.] 3 animals/sex/group with serial sampling.
[b.] 5 animals/sex/group with serial sampling.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; F, female; M, male</td></tr>
</table>

Source: Reviewer assessment.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; F, female; HPD, hours postdose; HR, heart rate; M, male; PID, prior to initiation of dosing; PR, pulse rate; QRS, end of PR interval to the end of S wave; QT, interval from beginning of QRS complex to the end of the T wave; QTc, QT interval corrected for heart rate; RR, respiratory rate

13.2.3.3. General Toxicology, Additional Studies (Nonpivotal)

13.2.3.3.1. Four-Day Oral Gavage Exploratory Toxicity Study of Nirmatrelvir in Wistar Han Rats (Study# 20GR250)

Administration of nirmatrelvir (PF-07321332) to Wistar Han rats once daily by oral gavage at doses of 30, 100, or 1000 mg/kg/day for 4 days resulted in no test article-related clinical observations, effects on body weight, hematology and clinical chemistry parameters, no macroscopic findings, and no microscopic test article-related findings in the bone marrow of the

sternum. Mean systemic exposure increased with increasing dose. Mean AUC_{24} values increased in a greater than dose-proportional manner suggestive of saturation of clearance mechanisms. There was no evidence for accumulation between Days 1 and 4.

13.2.3.3.2. Four-Day Oral Gavage Exploratory Toxicity Study of Nirmatrelvir in Cynomolgus Monkeys (Study# 20GR271)

Nirmatrelvir (PF-07321332) administered to male and female cynomolgus monkeys by oral gavage twice daily (BID) at doses of 30 (15 BID), 300 (150 BID), or 1000 (500 BID) mg/kg/day for 4 days was tolerated at all doses. Test-article-related emesis was observed at ≥300 mg/kg/day that was generally dose dependent and improved with repeat dosing. There were test article-related increases in fibrinogen (76 to 110%) and monocytes (102 to 145%) at ≥300 mg/kg/day on Day 5. At 1000 mg/kg/day on Day 5 there were also increases in white blood cells (103 to 112%) due to neutrophils (245 to 315%) and decreases in reticulocytes (63-79%). These changes at ≥300 mg/kg/day were indicative of an acute phase/inflammatory response with the decreased reticulocytes likely due to decreased production. Evidence of hemoconcentration or dehydration due to vomiting induced fluid loss were reported including increased red blood cells (6%), hemoglobin (4%), total protein (11%), due to increases in both albumin (10%) and globulin (11%), blood urea nitrogen (200%), and creatinine (57%) in high dose female group. Decreases in sodium (7%), potassium (20%), and chloride (23%), alongside increases in bilirubin (200%), triglycerides (167%), and glucose (60%) were also present. Mean systemic exposure increased with increasing dose. Based on mean AUC_{24} values, there was no evidence for accumulation between Days 1 and 4. There were no sex-related differences in systemic exposure (as assessed by C_{max} and AUC_{24}) across dose groups.

13.2.4. Genetic Toxicology

Table 67. Genetic Toxicology

Study Title/Study No.	Key Study Findings
PF-07321332: Bacterial Reverse Mutation Assay (20GR288) GLP compliance: Yes Study is valid: Yes	• TA98, TA100, TA1535, TA1537 and WP2uvrA strains were incubated with up to 5000 µg/plate with and without S9 metabolic activation. • No dose-related, two-fold increase in the number of revertant colonies was observed for the five tester strains. • PF-07321332 was not mutagenic under the experimental conditions.
PF-07321332: *In Vitro* Mammalian Cell Micronucleus Assay in TK6 Cells (20GR286) GLP compliance: Yes Study is valid: Yes	• Cultured human peripheral lymphocytes were exposed with up to 500 µg/mL for 4 or 27 hours without S9 metabolic activation and for 4 hours with up to 500 µg/mL with S9 metabolic activation. • PF-07321332 was considered negative for inducing chromosomal aberrations in in vitro human peripheral blood lymphocytes and was negative for clastogenicity under the experimental conditions.
Assay for Micronucleus Induction in Rat Bone Marrow	• Please see Section 13.2.3.2.1.

Reference ID: 5179402

Study Title/Study No.	Key Study Findings
Other genetic toxicology studies	Evaluation of the Mutagenic Activity of (b) (4) in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (Plate Incorporation and Pre-Incubation Methods) • (b) (4) was a step 1 product. • Direct plate assay – Dose-range from 52, 164, 512, 1600 to 5000 µg/plate was selected for the mutation assay with the tester strains, TA1535, TA1537 and TA98 in the absence and presence of S9-mix. – No increase in the number of revertants was observed upon treatment with the test item under all conditions tested. • Pre-incubation assay. – Test item was tested up to the dose level of 5000 µg/plate in the tester strains TA1535, TA1537, TA98, TA100 and WP2*uvrA* in the absence and presence of S9-mix. – No increase in the number of revertants was observed upon treatment with the test item under all conditions tested.

Source: Reviewer assessment.
Abbreviation: GLP, good laboratory practices; S9 fraction, contains metabolizing enzymes from the cytosol and microsomes

13.2.5. Carcinogenicity

Carcinogenicity studies were not conducted due to the short duration of nirmatrelvir treatment.

13.2.6. Reproductive and Developmental Toxicology

13.2.6.1. Fertility and Early Embryonic Development

13.2.6.1.1. Oral Gavage Male and Female Fertility Study of PF-07321332 in Wistar Han Rats (Study# 21GR146)

Key Study Findings

- No nirmatrelvir (PF-07321332)-related effects on male systemic toxicity or mortality, clinical observations, or effects on food consumption in females were observed. Although epididymal sperm maturation was not reported, no drug-related abnormalities were observed on male reproductive organs upon macroscopic examination. In females, non-adverse increase in body weights (compared to control animals) were observed at 1000 mg/kg/day prior to mating. No effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. The NOAEL for male and female fertility (and systemic toxicity) was 1000 mg/kg/day.

Table 68. Methods of Fertility and Early Embryo Development Study in Female and Male Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0 (vehicle), 60, 200 or 1000 mg/kg/day Daily dosing

Reference ID: 5179402

Parameter	Method Details
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension / vehicle consisting of (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rat / Wistar Han
Number/sex/group:	20/sex/group (blood samples were collected 0.5 hours post dose from 5 females and 5 males per group on Dosing Phase Day 10 to determine plasma drug concentration.)
Satellite groups:	None.
Study design:	Dosing begins at 14 days prior to the mating phase, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. Cesarean sections were performed on females on GD 14.
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States of America

Table 69. Observations and Results, Study 21GR146

Parameter	Major Findings
Mortality	No treatment-related findings.
Clinical signs	No treatment-related findings.
Food consumption	No treatment-related findings.
Body weights	PF-07321332-related, statistically higher body weight change was observed throughout the Premating Phase at 1000 mg/kg/day, resulting in nonsignificant slightly higher PF-07321332-related body weights on Premating Phase Day 14 (1.04x controls). No other treatment-related findings.
Sperm count	Not determined.
Sperm velocity	Not determined.
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]	No treatment-related findings.
Toxicokinetics Blood samples were collected 0.5 hours postdose on dosing Day 10.	**Table 70. Mean Concentration Data (ng/mL) on Dosing Phase Day 10 at 0.5 Hours Postdose for PF-07321332 in Wistar Han Rat Plasma**

Dose (mg/kg/day)	Sex	Mean	SD	n
60	Male	10400	3170	5
	Female	15800	4330	5
	Combined	13100	4580	10
200	Male	21000	5740	5
	Female	33000	11800	5
	Combined	27000	10800	10
1000	Male	19100	9050	5
	Female	46700	10500	5
	Combined	32900	17300	10

Source: Text Table 1 of the Toxicology Report from the sponsor.
Abbreviations: n, number of subjects in sample; SD, standard deviation

Source: Reviewer assessment.

13.2.6.2. Embryo-Fetal Development

13.2.6.2.1. Oral Gavage Embryo-Fetal Developmental Study of PF-07321332 in Pregnant Wistar Han Rats (Study# 21GR132)

Key Study Findings

- There were no nirmatrelvir-related maternal effects observed. In addition, no effects on fetal body weights or fetal external, visceral, or skeletal morphology were observed.

  The NOAEL for maternal and embryo-fetal development was 1000 mg/kg which corresponded to an $AUC_{0\text{-}24h}$ of 535,000 ng·h/mL for gestation day (GD) 17.

- The exposure margin was 7.8x based on the proposed human dose.

Table 71. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, or 1000 mg/kg/day Once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rats, Wistar Han
Number/sex/group:	20 females/group
Satellite groups:	None
Study design:	Dosing GD 6 to GD 17
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States of America

Table 72. Observations and Results, Study 21gr132

Parameter	Major Findings
Mortality	No drug-related fatality.
Clinical signs	No treatment-related findings.
Body weights	No treatment-related findings.
Necropsy findings Cesarean section data	There were no PF-07321332-related effects on cesarean section observations.
Necropsy findings Offspring	There were no PF-07321332-related external, visceral, or skeletal malformations or variations.

Parameter	Major Findings
Toxicokinetics Blood samples were collected on GD 17 at 0 (predose), 0.5, 1, 2, 4 hours postdose from 1-4 animals of each group.	**Table 73. TK Parameters for PF-07321332 in Rat EFD Study, GD 6 and 17**

Dose	C_{max} (ng/mL)			T_{max} (hours)			AUC_{24} (ng•h/mL)		
(mg/kg/day)	Mean	SD	n	Mean	SD	n	Mean	SD	n
100*	29000	11000	4	0.60	0.25	4	75500	12400	4
300	43200	14400	5	1.0	0.00	5	346000	92000	5
1000	65400	18700	5	1.1	0.55	5	535000	330000	5

Source: Table from Section10.3 of the Toxicology Report.
*Animal 009 had no viable fetuses and was excluded from mean calculations.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestational day; n, number of subjects in sample; SD, standard deviation; TK, toxicokinetic; T_{max}, time for drug to reach maximum concentration

Source: Reviewer assessment.
Note: (Kuwagata et al. 2019).
Abbreviations: GD, gestation day

13.2.6.2.2. Oral Gavage Embryo-Fetal Developmental Study of PF-07321332 in Pregnant New Zealand White Rabbits (Study# 21GR126)

Key Study Findings

- Lower (9%) fetal body weight was observed at the high dose of nirmatrelvir. No maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. Based on the lack of nirmatrelvir (PF-07321332)-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day.
- There were also no nirmatrelvir (PF-07321332)-related effects on fetal viability or morphological development in the study. However, the no observed effect level (NOEL) for developmental toxicity was 300 mg/kg/day based on lower fetal body weights at 1000 mg/kg/day.
  - At the NOEL for embryo-fetal development of 300 mg/kg, with $AUC_{0\text{-}96.5h}$ of 195,000 ng·h/mL for GD 19, the exposure margin was 2.8x based on human exposures.

Table 74. Methods of Oral Embryo-Fetal Developmental Study in Rabbit

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, or 1000 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension / (b) (4) and 0.5% (w/v) methylcellulose A4M in purified water
Species/strain:	Rabbits / New Zealand White
Number/sex/group:	20 females/group
Satellite groups:	None
Study design:	Dosing GD 7 to GD 19. The post-treatment period was from GD 20 to 29 and animals were euthanized on GD 29.
Conducting laboratory and location	Pfizer Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA

Parameter	Method Details
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: CT, Connecticut; GD, gestation day; GLP, good laboratory practices; USA, United States America

Table 75. Observations and Results

Parameter	Major Findings
Mortality	No treatment-related mortality.
Clinical signs	No treatment-related clinical signs.
Body weights	• At 1000 mg/kg/day, PF-07321332-related lower mean body weight change (0.58x control) was noted for the GD 7-20 interval in the absence of effects on body weight. • There were no other PF-07321332-related effects on maternal body weights, body weight change, corrected body weight, or corrected body weight change.
Necropsy findings Cesarean section data	There were no PF-07321332-related effects on cesarean section observations, including fetal viability.
Necropsy findings Offspring	• Treatment-related lower mean fetal body weight (0.91x control) was noted at 1000 mg/kg/day (statistically significant). • There were no PF-07321332-related fetal external, visceral, and skeletal observations.
Toxicokinetics Blood samples were collected on GD 19 at 0 (predose), 0.5, 1, 2, 4 hours post dose.	**Table 76. Toxicokinetic Parameters for PF-07321332 in Rabbit EFD Study**

Dose	C_{max} (ng/mL)			T_{max} (hours)			AUC_{24} (ng•h/mL)		
(mg/kg/day)	Mean	SD	n	Mean	SD	n	Mean	SD	n
100	17000	6100	5	0.60	0.22	5	98700	27400	5
300	42900	11100	5	0.90	0.65	5	195000	56800	5
1000	99600	46500	5	1.1	0.55	5	689000	206000	5

Source: Table in Section 10.3 of the Toxicology Study Report.
Abbreviations: AUC_{24}, area under the concentration-time curve to 24 hours; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestational day; n, number of subjects in sample; SD, standard deviation; T_{max}, time for drug to reach maximum concentration

Source: Reviewer assessment.
Abbreviations: EFD, embryo-fetal development; GD, gestation day

13.2.6.3. Pre- and Postnatal Development

13.2.6.3.1. An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats (Study# 21GR149)

Key Study Findings

- No adverse nirmatrelvir-related effects were observed in pregnant rats and F1 offspring at all dose levels. Body weight gain was decreased from PND 10 to 17 in the offspring at the highest dose of 1000 mg/kg/day, resulting in a decrease (8% in both males and females

compared to controls) of body weight at PND 17. No significant difference in body weight was noted at PND 28 (males) or PND 22 (females) to PND 56 (both sexes) and afterwards.

- NOAEL was identified at 1000 mg/kg/day for maternal toxicity.
- NOEL for developmental toxicity was 300 mg/kg/day due to an 8% decrease in body weight at PND 17. Drug concentrations in maternal and offspring plasma and breastmilk were not reported.

Table 77. Methods of Oral Gavage Pre- and Postnatal Developmental Toxicity Study in Rats

Parameter	Method Details
GLP compliance	Yes
Dose and frequency of dosing:	0, 100, 300, 1000 mg/kg Daily
Route of administration:	Oral gavage
Formulation/vehicle:	suspension / vehicle control: (b) (4) in 0.5% (w/v) methylcellulose A4M in Deionized Water; vehicle: (b) (4) and 0.5% (w/v) methylcellulose A4M in Deionized water
Species/strain:	Rat/ Wistar Han
Number/sex/group:	22 females per group
Satellite groups:	None
Study design:	PF-07321332 was administered once daily by oral gavage to time-mated female rats from Gestation Day (GD) 6 through Lactation Day (LD) 20. The growth, viability, and development of the F1 offspring, and reproductive performance of the F1 generation were assessed.
Conducting laboratory and location	(b) (4)
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer assessment.
Abbreviations: GLP, good laboratory practices; (b) (4); SC, subcutaneous

Table 78. Observations and Results

Generation	Major Findings
F0 dams	The only PF-07321332-related effects on the F0 generation was a lower mean body weight gain following the initiation of dosing at 1000 mg/kg/day and higher mean body weight gain during GD 19–20 and when the entire gestation dosing period (GD 6–20) was evaluated, which were not considered adverse due to the lack of impact on F0 body weights.
F1 generation	PF-07321332-related lower male and female pup body weight gains were observed at 1000 mg/kg/day during PND 10–17. As a result, mean F1 male and female pup body weights in this group were 0.92x the control group on PND 17. Mean male and female pup body weight gains at 1000 mg/kg/day were similar to the control group during PND 17–21 but mean absolute body weights remained slightly lower (0.93x and 0.94x the control group, respectively) on PND 21. The effects on F1 pups body weight parameters during PND 10–17 were considered PF-7321332-related but not adverse because the effect was transient, the pups had normal birth weights and growth was comparable to the control group prior to PND 10, and the body weight deficit began to resolve prior to weaning and did not persist to the postweaning period.

Generation	Major Findings
F2 generation	No assessment conducted
Toxicokinetics	Not determined.

Source: Reviewer assessment.
Abbreviations: GD, gestation day; PND, postnatal development

13.2.7. Other Toxicology Studies

13.2.7.1. Impurity Studies

13.2.7.1.1. A Two-Week Oral Gavage Impurity Qualification Toxicity Study of PF-07321332 in Wistar Han Rats (Study# 21GR206)

Nirmatrelvir (PF-07321332) was administered by oral gavage once daily for 14 days to male and female Wistar Han rats at a dose of 200 mg/kg/day with increased amounts of multiple impurities (b) (4) or without increased impurities.

Test article-related clinical observations were limited to salivation noted prior to dose administration on Day 14 in all groups administered nirmatrelvir with or without additional impurities.

When compared with controls, non-adverse findings in coagulation and clinical chemistry parameters were observed in male rats administered nirmatrelvir with and without additional impurities including prolongations in mean PT (1.05x to 1.07x) and APTT (1.10x-1.18x). In addition, compared with controls, male rats administered nirmatrelvir without additional impurities (Group 2) and male rats administered nirmatrelvir with the additional impurities (b) (4) (Group 3) had higher mean had higher mean globulin (1.04x to 1.07x) leading to higher total protein (1.04x), also resulting in a lower mean AG ratio in male rats administered PF-07321332 with additional impurities (Group 3; (b) (4)). This series of findings were not adverse due to the small magnitude of difference and lack of microscopic or clinical correlates.

Non-adverse test article-related higher liver weights (1.11x to 1.18x) were noted in females administered nirmatrelvir without additional impurities (Group 2) and with additional impurities (b) (4) (Group 4), compared with controls. These weight differences were not adverse due to the small magnitude of difference and lack of macroscopic and/or microscopic correlates.

There were no consistent sex-related differences in systemic exposure for nirmatrelvir observed at 0.5 hours post-dose, and exposures were similar across groups administered nirmatrelvir with or without additional impurities.

Based on the data, impurities are qualified at the levels in Table 79.

Table 79. PAXLOVID Drug Substance Organic Impurity Specifications

(b) (4)

14. Clinical Pharmacology

14.1. In Vitro Studies

Protein Binding

Protein binding of nirmatrelvir at a concentration of 0.3, 1, 3, and 10µM in human plasma was evaluated using equilibrium dialysis (Study PF 07321332_23Nov20_010657). The binding of nirmatrelvir to human plasma proteins was not concentration dependent. The mean fraction unbound of nirmatrelvir in human plasma proteins at concentration of 0.3, 1, 3, and 10µM was 0.296, 0.300, 0.311, and 0.333, respectively.

Blood to Plasma Partitioning

Human whole blood samples were used to measure red blood cell partitioning of nirmatrelvir (Study PF-07321332_18Nov20_100444). Nirmatrelvir mean (standard deviation) blood to plasma ratio was estimated to be 0.60 (0.024).

Metabolism

The metabolism of nirmatrelvir was evaluated in human liver microsomes and human hepatocytes (Study PF-07321332_09Nov20_084546). The primary metabolite was M4, which results from a mono-hydroxylation at the C-5 position of the pyrrolidinone ring. The other sites of oxidation resulted in the formation of minor metabolites. Across a panel of human recombinant CYPP450 enzymes, all oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts.

Metabolite M5 was detected as a minor metabolite at trace levels in human circulation and excreta when nirmatrelvir was co-administered with ritonavir. M5 is formed through hydrolytic cleavage across an amide bond in nirmatrelvir. Metabolite M7, the acyl-glucuronide conjugate of M5, was also identified in human urine in trace amounts (Study PF07321332_14Sep21_021626).

In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was the major contributor (fm = 0.99) to the oxidative metabolism of nirmatrelvir. (Study PF07321332_21Nov20_072016).

When co-administered with ritonavir, oxidative metabolism was a minor component of overall nirmatrelvir clearance. Unchanged nirmatrelvir was the predominant drug-related entity in circulation in plasma from healthy adults administered with a single oral dose of 300 mg nirmatrelvir in the presence of ritonavir (Study C4671001, Cohort 9). Only trace amounts of M4, M5, and M8 were detected in circulation when nirmatrelvir was co-administered with ritonavir (Study PF-07321332_08Sep21_090141).

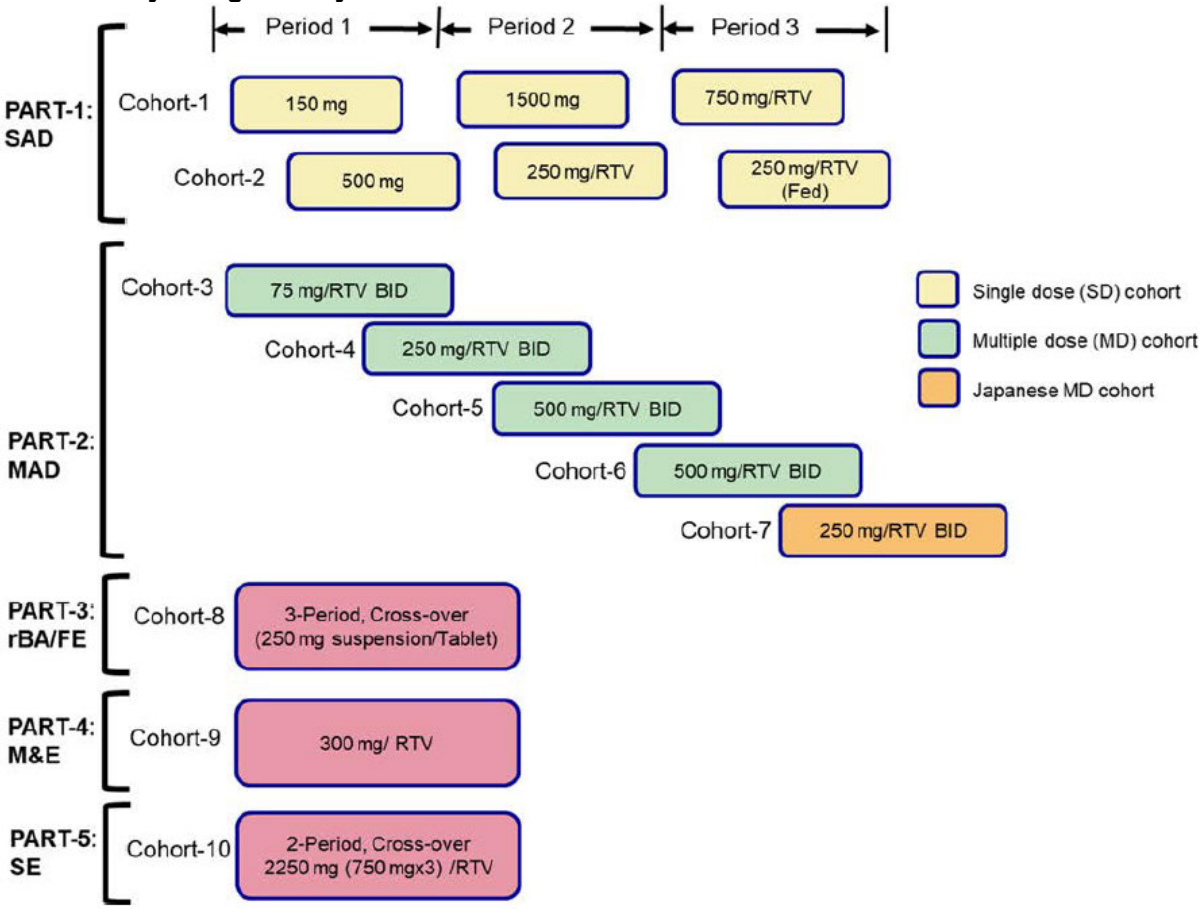
Nirmatrelvir as a Substrate, Inhibitor, and Inducer of Drug-Metabolizing Enzymes and Transporters

See Table 47 and Table 48 in Section 8.2.2.1.

14.2. In Vivo Studies

Study 1001 was the first-in-human study with nirmatrelvir alone and nirmatrelvir co-administered with ritonavir. This was a 5-part study consisting of part 1: single ascending dose, part 2: multiple ascending dose, part 3: relative bioavailability/food effect, part 4: metabolism and excretion, and part 5: supratherapeutic exposure (Figure 20).

Figure 20. Study Design: Study 1001



Source: Study 1001.
Abbreviations: BID, twice daily; MAD, multiple ascending dose; MD, multiple dose; M&E, metabolism and excretion; rBA/FE, relative bioavailability/food effect; RTV, ritonavir; SAD, single ascending dose; SE, supratherapeutic exposure

Part 1: Single Ascending Dose

Part 1 evaluated a single dose of 150 mg, 500 mg, and 1500 mg nirmatrelvir alone and at 250 mg and 750 mg nirmatrelvir dose with ritonavir 100 mg (dosed at -12hours, 0hours, and 12hours). The effect of food was also evaluated in a cohort of subjects receiving nirmatrelvir 250 mg + ritonavir 100mg at -12, 0 and 12 hours with a high-fat meal. A total of 12 subjects were included in 2 cohorts, each consisting of 4 active and 2 placebo subjects with three periods in each cohort (Table 80). A washout interval of at least 5 days was given between dosing to each subject. Nirmatrelvir and placebo were administered as an extemporaneously prepared oral suspension, and ritonavir was administered as the 100 mg commercial tablet.

Table 80. Study 1001, Part 1: SAD Dosing Scheme

Cohort	N	Period 1	Period 2	Period 3
1	2	150 mg	1500 mg	Placebo/ritonavir
	2	150 mg	Placebo	750 mg/ritonavir
	2	Placebo	1500 mg	750 mg/ritonavir
2	2	500 mg	250 mg/ritonavir	250 mg/ritonavir (fed)
	2	500 mg	Placebo/ritonavir	Placebo/ritonavir (fed)
	2	Placebo	250 mg/ritonavir	250 mg/ritonavir (fed)

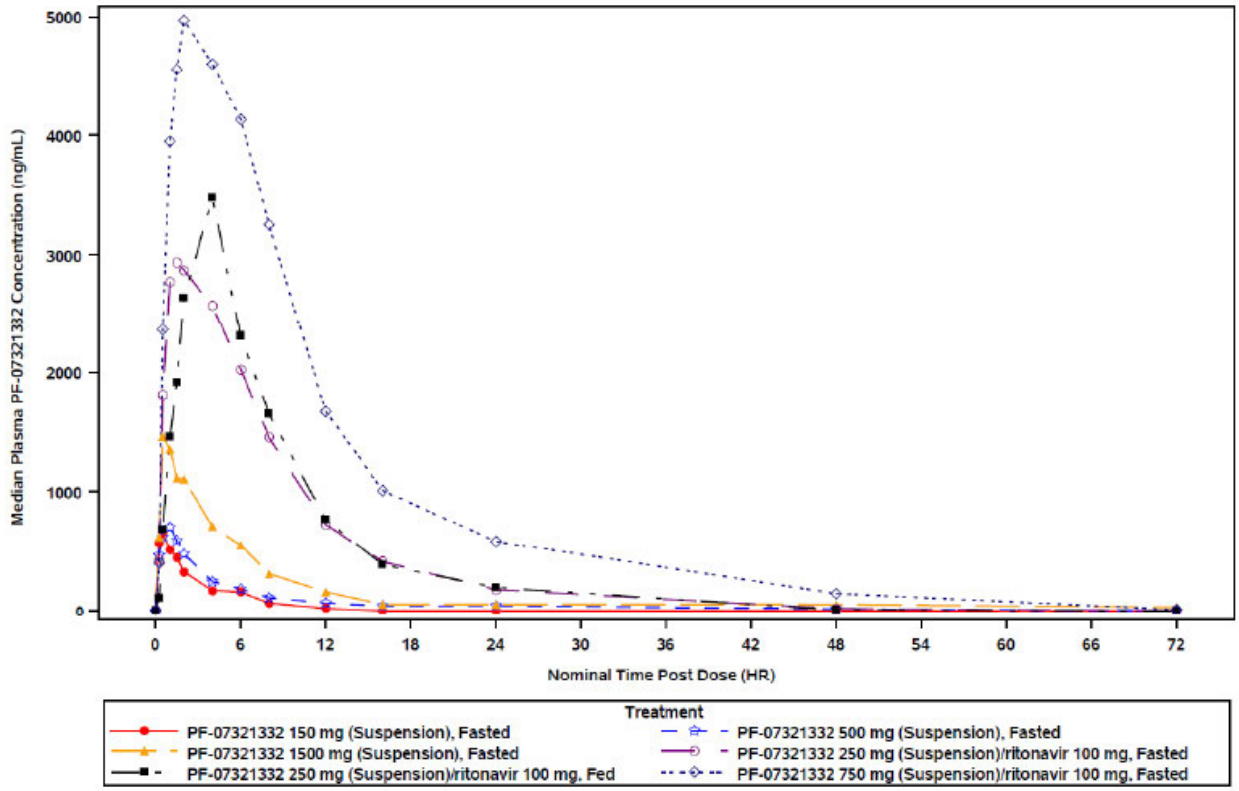
Source: Study 1001.
Abbreviations: N, total number of subjects; SAD, single ascending dose

Blood samples were collected pre-dose and up to 96 hours post dose for measurement of nirmatrelvir plasma concentrations. At the nirmatrelvir dose of 1500 mg (Cohort-1, Period 2), urine and feces samples were collected up to 120 hours post-dose for fluorine-19 nuclear magnetic resonance (^{19}F-NMR) spectroscopy and metabolite profiling.

Nirmatrelvir exposures increased in a less-than dose-proportional manner following administration of nirmatrelvir as an oral suspension at doses of 150 mg, 500 mg, and 1500 mg without ritonavir and 250mg and 750 mg nirmatrelvir co-administered with 100 mg ritonavir. Mean nirmatrelvir plasma concentration-time profiles and PK parameters by treatment are summarized in Figure 21 and Table 81, respectively. Ritonavir administered with nirmatrelvir as a CYP3A inhibitor resulted in higher systemic concentrations of nirmatrelvir (Table 82).

Following administration of a 250 mg oral suspension of nirmatrelvir co-administered with ritonavir 100 mg under fed and fasted conditions, the test/reference ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUC_{last} and C_{max} were 101.53% (90.18%, 114.31%) and 115.30% (99.36%, 133.79%) respectively, for nirmatrelvir/ritonavir fed treatment (Test) compared to nirmatrelvir/ritonavir fasted treatment (Table 81).

Figure 21. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Single Oral Doses of Nirmatrelvir Alone or Enhanced With Ritonavir in Part 1, Study 1001



Source: Study 1001.

Table 81. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Part 1: SAD, Study 1001

Parameter [a,b]	NIR 150 mg (N=4)	NIR 500 mg (N=4)	NIR 1500 mg (N=4)	NIR 250 mg/ritonavir 100 mg (N=4)	NIR 250 mg/ritonavir 100 mg (Fed; N=4)	NIR 750 mg/ritonavir 100 mg (N=4)
N1, N2[c, d]	4, 3	4, 2	4, 0	4, 4	4, 4	4, 4
AUC_{inf} (ng.hr/mL)	2247 (42)	5480, 5450	NR	28220 (14)	28640 (17)	66760 (45)
AUC_{last} (ng.hr/mL)	2125 (34)	3753 (29)	10870 (47)	27600 (13)	28020 (16)	64230 (39)
CL/F (L/hr)	66.83 (43)	91.2, 91.8	NR	8.865 (14)	8.735 (17)	11.22 (45)
C_{max} (ng/mL/mg)	667.7 (28)	674.4 (38)	1538 (32)	2882 (25)	3323 (13)	5086 (25)
$t_{1/2}$ (hr)	2.023 ± 0.54556	18.5, 25.6	NR	6.935 ± 1.0794	6.005 ± 1.6502	12.86 ± 8.4196
T_{max} (hr)	0.634 (0.550 - 1.50)	1.00 (0.517 - 1.00)	1.00 (0.533 - 2.00)	2.75 (1.50 - 4.00)	4.00 (4.00 - 4.00)	2.00 (1.50 - 4.00)
Vz/F (L)	190.6 (36)	2440, 3390	NR	87.98 (28)	73.48 (47)	181.9 (35)

Source: Study 1001.
Note: Summary statistics were not presented if fewer than 3 participants had reportable parameter values.
[a.] Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for t1/2
[b.] Individual values were listed when there were less than 3 evaluable measurements
[c.] N1 = Number of participants contributing to the summary statistics.
[d.] N2 = Number of participants where t1/2, AUC_{inf}, $AUC_{inf(dn)}$, CL/F and Vz/F were determined
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of subjects in the treatment group; NIR, nirmatrelvir; NR, not reported; PK, pharmacokinetic; SAD, single ascending dose; $T_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; Vz/F, apparent volume of distribution

Table 82. Single Dose Pharmacokinetics of Nirmatrelvir Alone vs. Nirmatrelvir With Ritonavir in Healthy Subjects,Study 1001 (Oral Suspension Formulation)

	Geometric Mean (%CV)	
Treatment	**AUC_{last} (ug.hr/mL)**	**C_{max} (ug/mL)**
Nirmatrelvir alone[a]	3.32	0.88
Nirmatrelvir+Ritonavir[b]	27.6	2.88

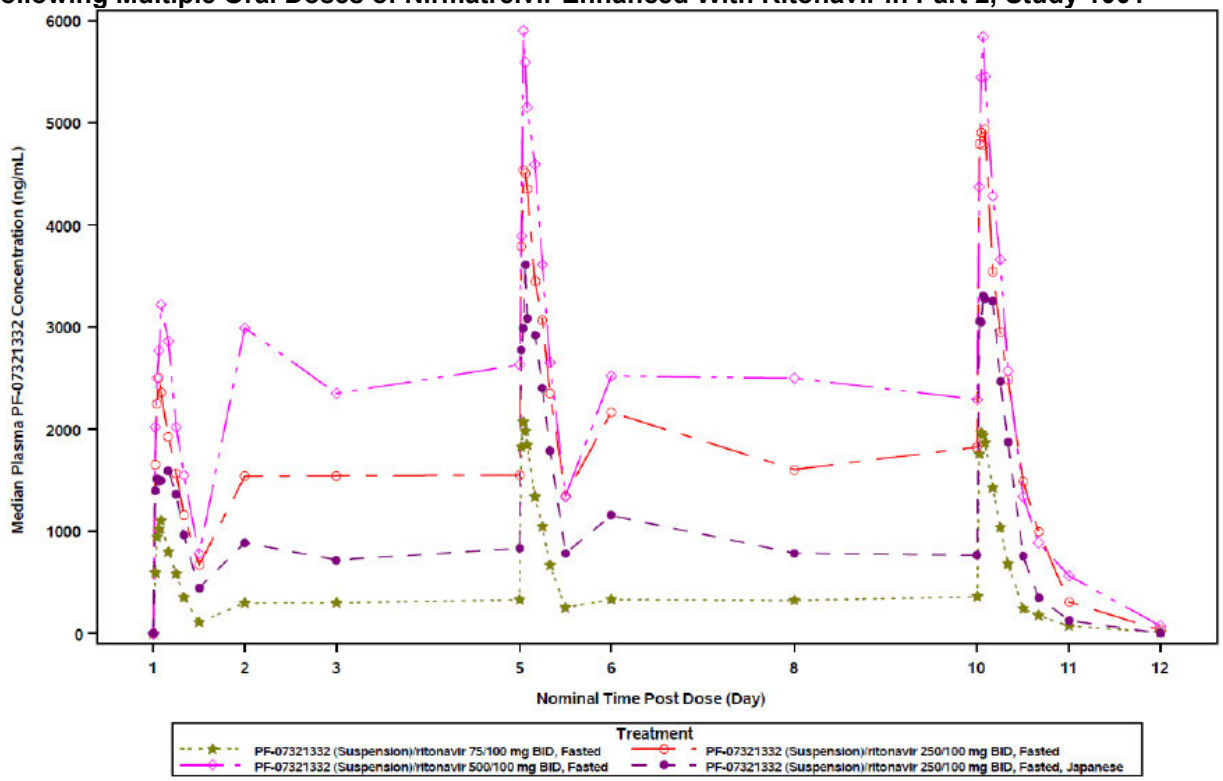
Source: Study 1001.
[a.] 250 mg (oral suspension formulation)
[b.] 250 mg (oral suspension formulation with 100 mg ritonavir (tablet formulation) administered together
Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation

Part 2: Multiple Ascending Dose

In Part 2, the multiple dose pharmacokinetics of nirmatrelvir were evaluated in healthy subjects. Nirmatrelvir was administered twice daily for 10 days at doses of 75mg, 250 mg, and 500 mg or placebo. All subjects received ritonavir 100 mg at -12hours, 0hours and 12hours with respect to nirmatrelvir dosing. The dosing regimen of 250mg/100mg twice daily for 10 days was also evaluated in a cohort of Japanese subjects (n=6) to compare the PK with non-Japanese subjects. Six subjects were enrolled per cohort, (4 subjects randomized to nirmatrelvir plus 2 subjects to placebo) and all subjects received the study drug under fasted conditions. A total of 29 subjects were enrolled, 6 were white (21%), 16 were black (55%) and 7 (24%) identified as Asian. Blood samples were collected up to 12 days post dose for measurement of nirmatrelvir plasma concentrations**.**

Following multiple oral doses of nirmatrelvir enhanced with ritonavir, nirmatrelvir exposure on Days 1, 5, and 10 increased in a less than dose proportional manner with an increase in dose. Steady state was achieved around Day 2 for all treatments. Nirmatrelvir accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10. Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} (R_{ac}) and C_{max} (R_{ac},C_{max}) on Day 10, across all treatments. Urinary recovery of unchanged nirmatrelvir was 64%, 52% and 23% for the 75 mg, 250 mg, and 500 mg nirmatrelvir enhanced with 100 mg ritonavir. Plasma nirmatrelvir concentration-time profiles across all dosing groups and PK parameters by treatment and day are summarized in Figure 22 and Table 83, respectively.

Figure 22. Median Plasma Nirmatrelvir Concentration-Time Profiles Across All Dosing Days Following Multiple Oral Doses of Nirmatrelvir Enhanced With Ritonavir in Part 2, Study 1001



Source: Study 1001.
Abbreviations: BID, twice daily

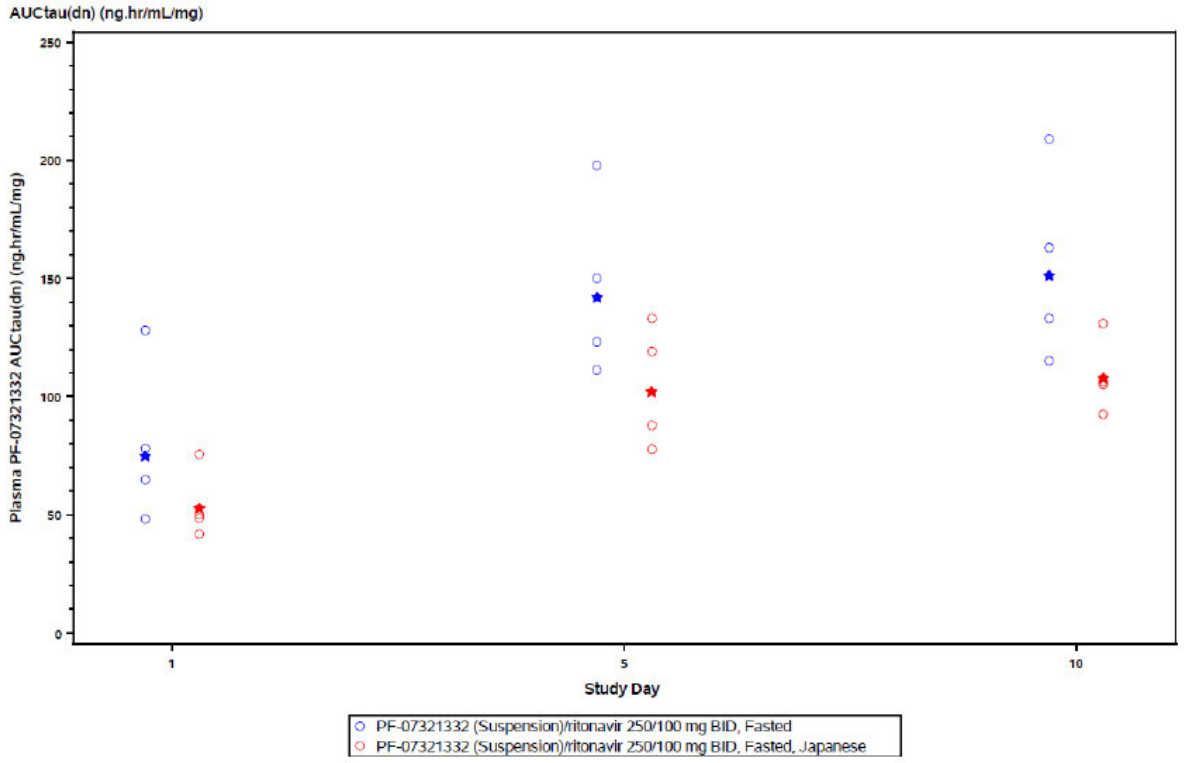
Table 83. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters, Part-2: MAD, Study 1001

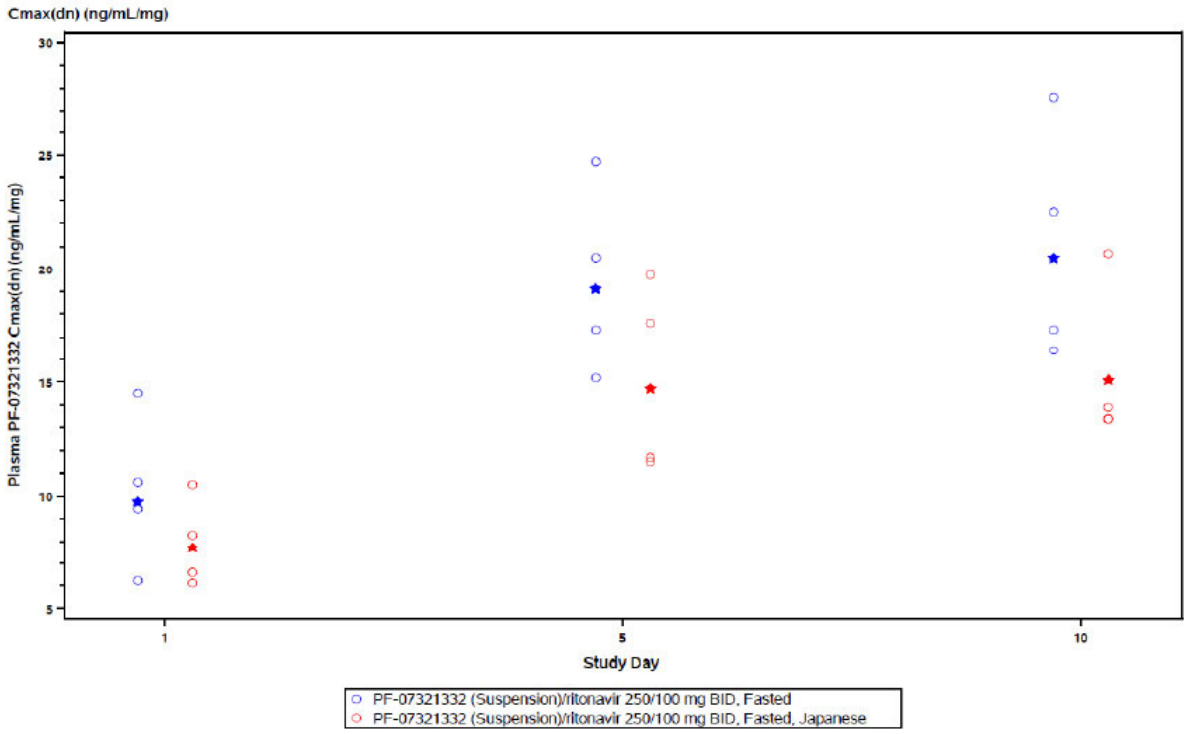
Parameter (unit)	Nirmatrelvir/ Ritonavir 75/100 mg BID (N=4)	Nirmatrelvir/ Ritonavir 250/100 mg BID (N=4)	Nirmatrelvir/ Ritonavir 500/100 mg BID (N=7)	Nirmatrelvir/ Ritonavir 250/100 mg BID Japanese (N=4)
Day 1				
AUC_{tau} (ng.hr/mL)	6017 (33)	18700 (43)	22610 (37)	13130 (26)
C_{max} (ng/mL)	1042 (28)	2435 (36)	3051 (32)	1925 (25)
T_{max} (hr)	1.75 (1.00 - 2.00)	1.50 (1.00 - 4.00)	2.00 (1.50 - 2.17)	2.75 (1.00 - 4.02)
Day 5				
AUC_{tau} (ng.hr/mL)	12570 (17)	35560 (26)	38150 (23)	25480 (26)
C_{max} (ng/mL)	2224 (27)	4774 (21)	5296 (21)	3674 (28)
T_{max} (hr)	1.00 (1.00 - 1.50)	0.750 (0.500 - 1.50)	1.50 (1.00 - 2.02)	1.26 (1.00 - 2.02)
Day 10				
AUC_{tau} (ng.hr/mL)	12650 (16)	37780 (27)	39780 (20)	26930 (15)
C_{max} (ng/mL)	2055 (14)	5123 (24)	5607 (17)	3772 (21)
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)

Source: Study 1001.
Abbreviations: AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; MAD, multiple ascending dose; N, total number of subjects in treatment group; T_{max}, time for drug to reach maximum concentration

The geometric mean dose-normalized AUC_{tau} and C_{max} of nirmatrelvir was approximately 30% and 21% to 26% lower in Japanese subjects compared to that observed for non-Japanese subjects across all days (Table 83 and Figure 23). This exposure difference is not expected to be clinically significant. Drug accumulation on Day 10 based on AUC_{tau} (R_{ac}) and C_{max} ($R_{ac,Cmax}$) ratios was similar between the Japanese and non-Japanese participants. Urinary recovery of unchanged nirmatrelvir was similar between Japanese and non-Japanese participants.

Figure 23. Individual and Geometric Mean Plasma Nirmatrelvir Dose Normalized AUC_{tau} (Upper Panel) and C_{max} (Lower Panel) Values Following Multiple Oral Doses of Nirmatrelvir Enhanced With Ritonavir in Part 2: MAD, Japanese Cohort Comparison, Study 1001





Source: Study 1001.
Abbreviations: AUC_{tau}, area under concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; MAD, multiple ascending dose

Part 3: Relative Bioavailability and Food Effect

Part 3 was a randomized open-label study to evaluate relative bioavailability and food effect of an early 250 mg oral tablet formulation relative to the 250 mg oral suspension used in part 1 and part 2. Subjects (n = 12 per group) received a 250 mg nirmatrelvir tablet as a single dose in either the fasted or fed state, or a single 250 mg dose of the nirmatrelvir suspension (without ritonavir). The 250 mg tablet strength when dosed with ritonavir was expected to be in the efficacious dose range and was chosen based on the PK, safety and tolerability data from single ascending dose (SAD) and multiple ascending dose (MAD) cohorts, and the available tablet strength.

Under fasting conditions, nirmatrelvir plasma exposure for the tablet was lower compared to the suspension following a single 250 mg oral dose of nirmatrelvir, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively (Table 84).

Nirmatrelvir plasma exposure was higher for the fed treatment following administration of a 250 mg high-fat, high-calorie meal, with approximately 1.5 and 2.4-fold higher geometric mean AUC_{last} and C_{max} values for fed treatment compared to the fasted treatment, respectively (Table 85).

Table 84. Statistical Summary of Plasma Nirmatrelvir PK Parameters – Relative Bioavailability, Part 3, Study 1001

	Adjusted Geometric Mean			
Parameter	Nirmatrelvir 250 mg Tablet (Fasted)	Nirmatrelvir 250 mg Suspension (Fasted)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	2955	3884	0.76	(0.60, 0.96)
AUC_{last} (ng.hr/mL)	2695	3318	0.81	(0.69, 0.95)
C_{max} (ng/mL)	497.8	883.1	0.56	(0.43, 0.73)

Source:Study 1001.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve tfrom the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Table 85. Statistical Summary of Plasma Nirmatrelvir PK Parameters – Food Effect, Part 3, Study 1001

	Adjusted Geometric Means			
Parameter	Nirmatrelvir 250 mg Tablet (Fed)	Nirmatrelvir 250 mg Tablet (Fasted)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	4337	2955	1.47	(1.18, 1.81)
AUC_{last} (ng.hr/mL)	4012	2695	1.49	(1.27, 1.75)
C_{max} (ng/mL)	1219	497.8	2.45	(1.89, 3.18)

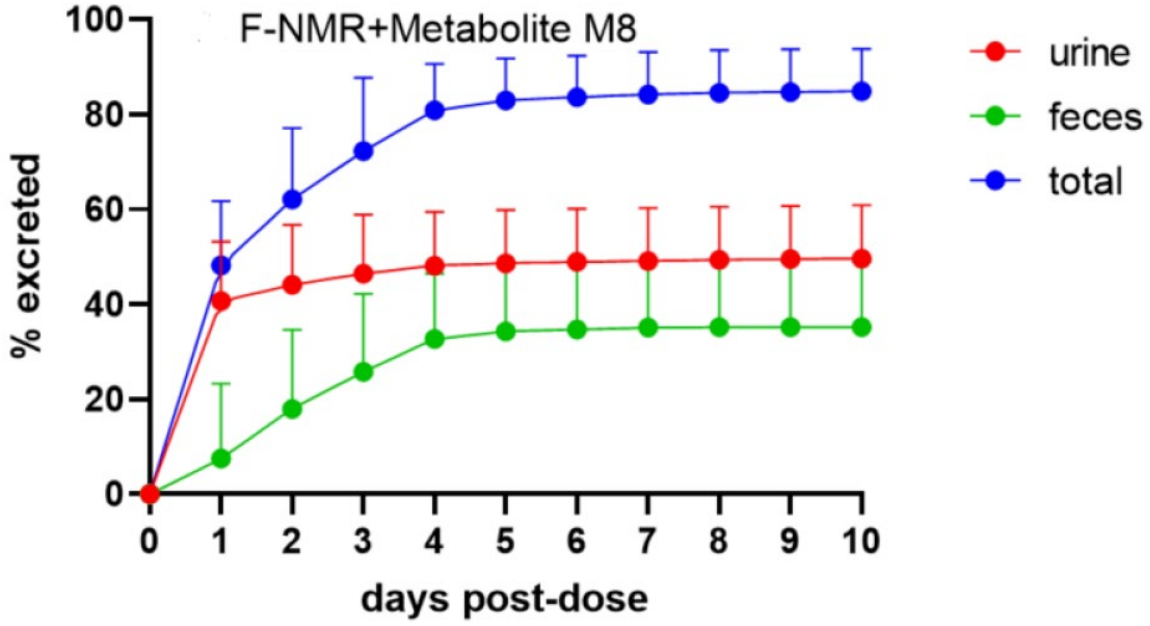
Source:Study 1001.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve tfrom the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Part 4: Metabolism and Excretion

Part 4 was conducted to determine the excretion of drug-related material in urine and feces after a single oral administration of nirmatrelvir with ritonavir. A single oral dose of 300 mg nirmatrelvir oral suspension co-administered with ritonavir (4 doses of 100 mg at -12, 0, 12, and 24 hours relative to nirmatrelvir), was administered to a total of 6 healthy subjects. Excretion of nirmatrelvir-related material in urine and feces was quantified using ^{19}F-NMR and high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) methods.

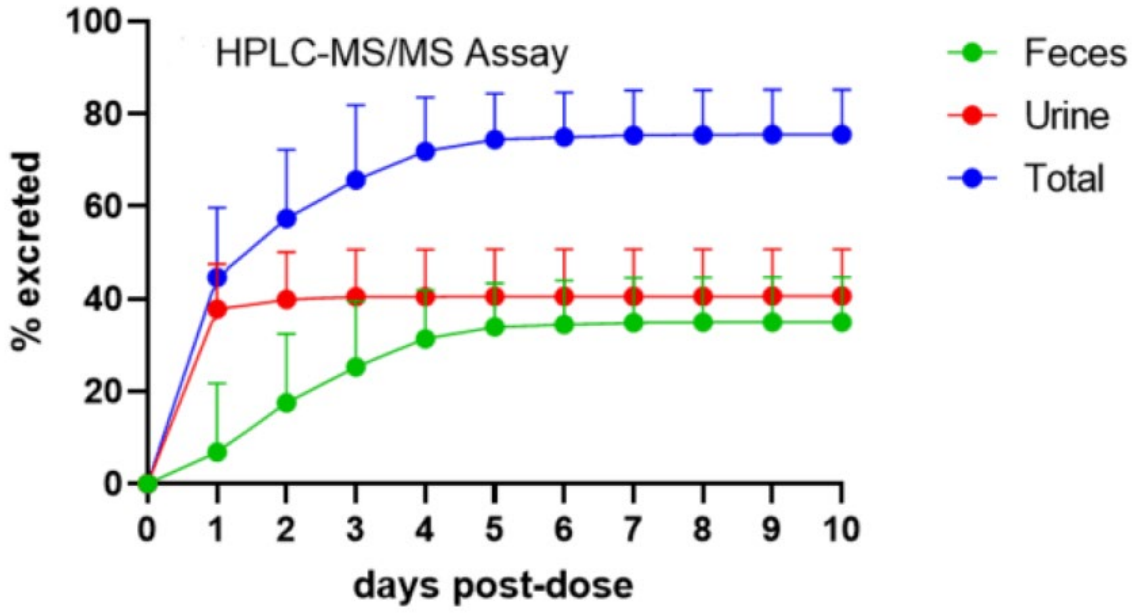
Overall mean ± SD (range) mass recovery of nirmatrelvir-related material in excreta (urine and feces) was 84.9% ± 8.9% (70.7%, 95.5%), which included 80.7% ± 8.0% nirmatrelvir by quantitative ^{19}F-NMR and 4.2% ± 1.3% excreted as metabolite M8 (^{19}F-NMR silent due to loss of trifluoroacetyl group) quantified by UHPLC-HRMS (ultra-high-performance liquid chromatography-high resolution mass spectrometry). The excretion into urine and feces was 49.6% and 35.3% of the dose, respectively (Figure 24). Quantifying nirmatrelvir and M5 (most prevalent metabolite in preliminary metabolite profiling) by HPLC-MS/MS showed overall mean ± SD mass recovery of 75.6 ± 9.7% with 40.6% and 35.0% excretion into urine and feces, respectively (Figure 25).

Figure 24. Cumulative Mean (+ SD) Excretion Nirmatrelvir-Related Material in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir Measured by ^{19}F-NMR Spectroscopy



Source:Study 1001.
Abbreviations: M8, metabolite 8; NMR, nuclear magnetic resonance; SD, standard deviation

Figure 25. Cumulative Mean (+ SD) Excretion of Nirmatrelvir and M5 in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir Using HPLC-MS/MS



Source: Study 1001.
Abbreviations: HPLC, high-performance liquid chromatography; M5, metabolite 5; MS/MS, tandem mass spectrometry; SD, standard deviation

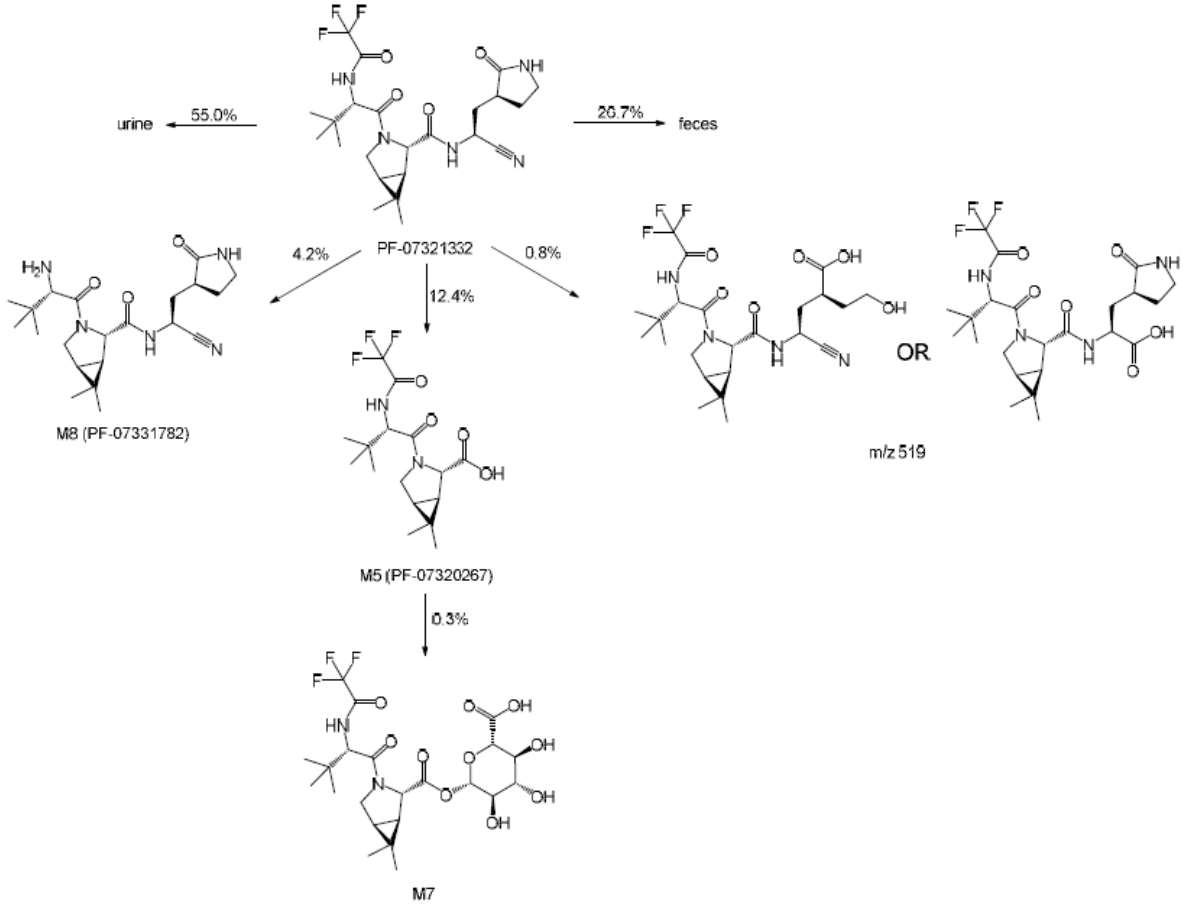
In plasma, the only drug-related entity quantifiable by ^{19}F-NMR was unchanged nirmatrelvir. In excreta, nirmatrelvir was the predominant drug-related entity. Unchanged nirmatrelvir represented the majority of the drug-related material, with 55.0% in urine and 27.5% in feces. These values were calculated based on dose normalization to 95.8% mass balance (i.e., 100% minus the 4.2% of dose comprised by non-fluorine containing metabolite M8). Metabolite M5, arising via hydrolysis, was present at 12.1% of dose with almost all in the feces. All other fluorine-containing metabolites were minor (<1% of dose), and M8 was 4.2% of dose (Table 86). A metabolic scheme for nirmatrelvir is shown in Figure 26.

Table 86. Summary of Metabolites of Nirmatrelvir in Urine and Feces of Healthy Participants Following Oral Administration of Nirmatrelvir Suspension Enhanced With Ritonavir

	% of Normalized Dose		
Metabolite	**Urine**	**Feces**	**Total**
Nirmatrelvir	55	27.5	82.5
M5	0.4	11.7	12.1
M8	0.3	ND	0.3
m/z 519	ND	0.8	0.8
M8	2.6	1.6	4.2
Total	58.4	41.6	100

Source: Study 1001.
Abbreviations: M, metabolite; m/z, mass-to-charge ratio; ND, not detected

Figure 26. Summary of Profile of Nirmatrelvir Metabolism and Disposition in Healthy Participants

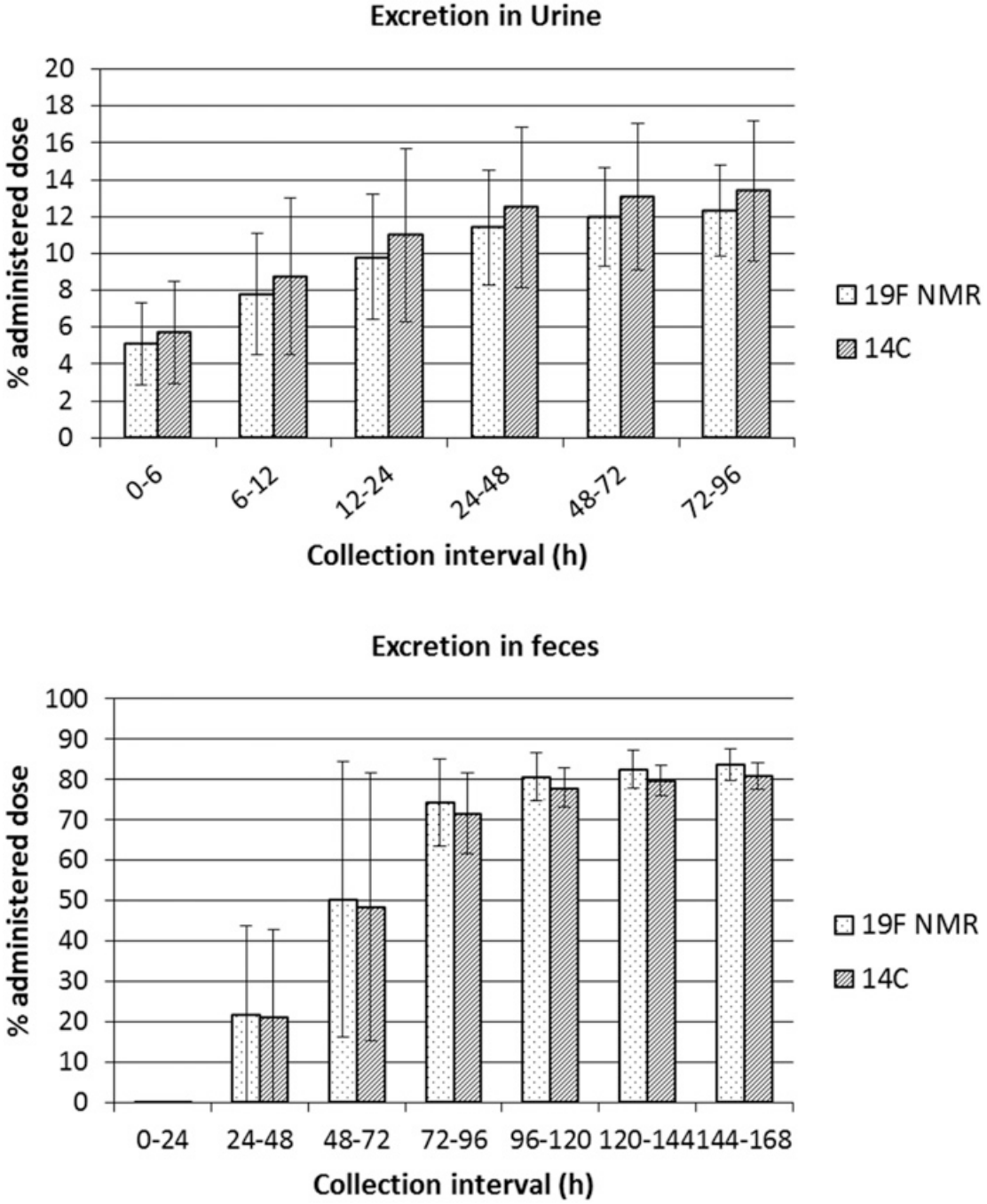


Source: Study 1001.
Abbreviations: M, metabolite; m/z, mass-to-charge ratio

The review team found the use of ^{19}F-NMR and UHPLC-HRMS to be an acceptable alternative to a radiolabeled mass balance study given 1) a published clinical study cross validating ^{14}C data with that obtained by ^{19}F-NMR and 2) additional nonclinical and clinical data provided by the Applicant to quantify the absorption, distribution, metabolism, and excretion (ADME) properties of nirmatrelvir.

The capability of ^{19}F-NMR to characterize the ADME properties of a drug was demonstrated in a clinical study by James et al (James et al. 2017). In this study, remaining samples from a ^{14}C human mass balance study conducted on Alpelisib, a compound for the treatment of solid tumors, were used to cross-validate the data obtained by ^{19}F-NMR. Mean cumulative excretion of the dose in urine and feces was comparable between the ^{14}C radiolabeled and ^{19}F-NMR samples (Figure 27). Comparable data was also obtained for total drug related material in plasma and metabolite profiling and identification in plasma and excreta.

Figure 27. Mean Cumulative Excretion of Dose in Urine and Feces After a Single Oral Dose of 400 mg [^{14}C]BYL719 (Alpelisib) to Four Healthy Volunteers, Determined by Liquid Scintillation Counting and ^{19}F NMR



Source: (James et al. 2017).
Abbreviations: NMR, nuclear magnetic resonance

Additional nonclinical and clinical data provided by the Applicant included 1) characterization of the metabolic profile in animals and 2) Phase 1 urine and plasma data. Animal data showed rats and monkeys to have a similar metabolic profile, with no notable human specific metabolites or metabolite specific toxicities reported (see Section 13). Phase 1 plasma and urine data showed similar urinary recovery, with 52% in the MAD arm of Study 1001 (250 mg nirmatrelvir/ 100

mg ritonavir dose) and 31% in subjects with normal renal function in Study 1011 (100mg nirmatrelvir/ 100 mg ritonavir dose), excreted as unchanged nirmatrelvir, respectively.

Part 5: Supratherapeutic Exposure

Part 5 was a double-blind (participant and investigator blinded and sponsor unblinded), randomized, 2-sequence, cross-over design to explore safety, tolerability, and PK at supratherapeutic exposure of nirmatrelvir. For each period, subjects received 2250 mg of nirmatrelvir as 3 split doses of 750 mg at 0 hours, 2 hours, and 4 hours, pharmacokinetically enhanced with ritonavir (3 doses of 100 mg at -12, 0 and 12 hours relative to nirmatrelvir) or placebo in the fasted state on Day 1 (n = 10 per group). Doses were split in this part of the study to achieve supratherapeutic exposures of nirmatrelvir that were not achieved in the SAD and MAD cohorts due to the less than dose proportional increase in exposure. Plasma samples for measurement of nirmatrelvir PK were obtained pre-dose and up to 96 hours post dose or at early termination if applicable.

Nirmatrelvir pharmacokinetic parameters following a supratherapeutic dose of 2250 mg administered with ritonavir are presented in Table 87. The safety data, including adverse events (AEs), laboratory abnormalities, vital signs, and ECGs indicate that nirmatrelvir has an acceptable safety and tolerability profile in healthy adult subjects at supratherapeutic exposures.

Table 87. Descriptive Summary of Plasma Nirmatrelvir PK Parameters Following Administration of Nirmatrelvir (Suspension)/Ritonavir 100 mg in Part 5, Study 1001

Parameter	Measurement
N	10
AUC_{inf} (µg.hr/mL)	188.82 (35)
CL/F (L/hr)	3.970 (35)
C_{max} (µg/mL)	15.94 (27)
$T_{1/2}$ (hr)	7.45 ± 2.94
T_{max} (hr)	5.0 (3.02 – 6.03)

Source: Study 1001.
Note: Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for t1/2
Note: Nirmatrelvir 2250 mg Was Divided Into Three Doses of 750 mg Administrated at 0h, 2h and 4h; Ritonavir Dosed at -12h, 0h and 12h post-dose
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of subjects in the treatment group; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration

Renal Impairment

In Study 1011, the PK of nirmatrelvir was evaluated in the fasted state after a single 100 mg dose of nirmatrelvir co-administered with 100mg ritonavir -12, 0 and 12 hours relative to nirmatrelvir in the following groups:

- Mild renal impairment: eGFR 60 to <90 mL/min
- Moderate renal impairment: eGFR >30 to <60 mL/min
- Severe renal impairment: eGFR <30 and not requiring dialysis
- Normal renal function: eGFR >90 mL/min

The 100 mg nirmatrelvir dose (one third the total daily dose) was chosen due to the less-than dose-proportional increase in exposures within the 250 mg to 750 mg dose range evaluated, and

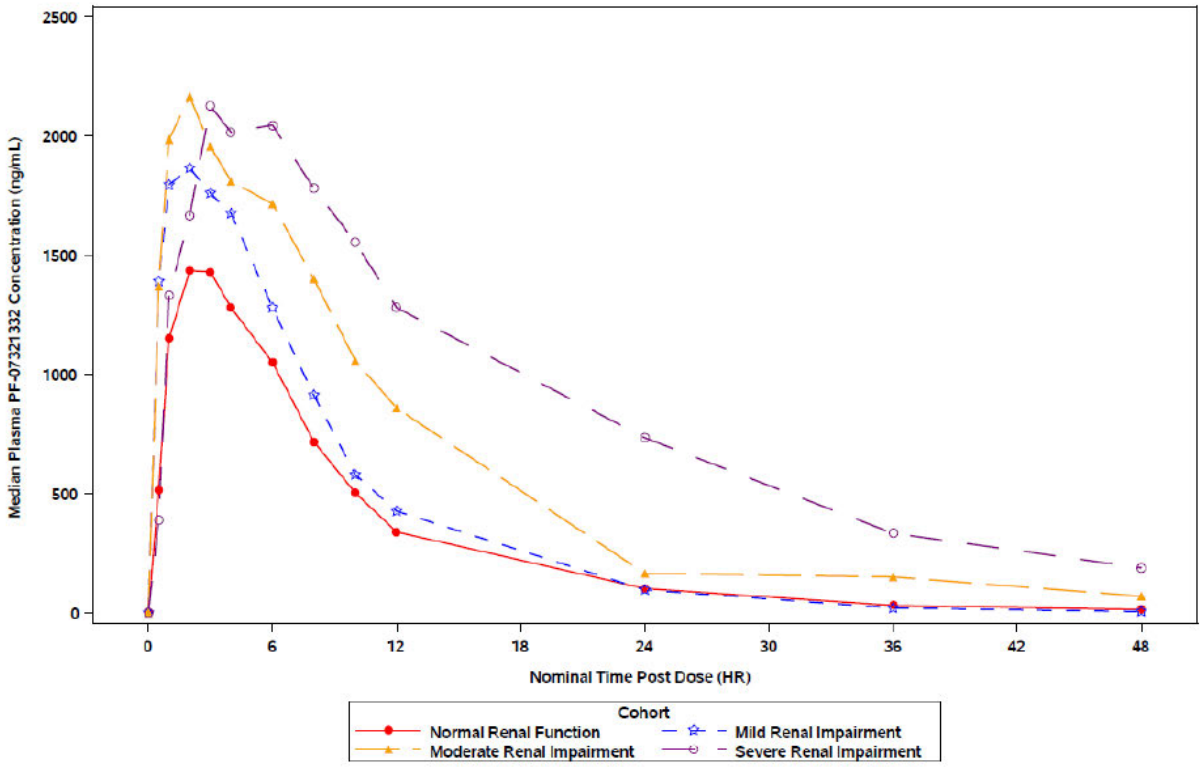
the anticipated higher exposures in renal impairment. As ritonavir is not eliminated renally and is not expected to be significantly altered by renal impairment, no dose reduction of ritonavir was considered necessary for subjects with renal impairment.

Blood and urine samples were collected through 48 hours for measurement of nirmatrelvir in plasma. Given that nirmatrelvir has a low extent of plasma protein binding (approximately 69%), a description and analysis of nirmatrelvir PK in terms of total concentrations is sufficient since changes in PK resulting from alterations in protein binding due to impaired renal function are generally expected to be small relative to those in patients with normal renal function.

Nirmatrelvir systemic exposure increased with increasing severity of renal impairment, with mean AUC_{inf} values of approximately 24%, 87%, and 204% higher for the mild, moderate, and severe renal impairment groups, respectively, compared to the normal renal functional group. Geometric mean C_{max} values also increased approximately 30%, 38%, and 48% for the mild, moderate, and severe renal impairment groups, respectively, compared to the normal renal functional group. See Figure 28, Table 88 and Table 89.

Urinary recovery of unchanged nirmatrelvir was 31.2%, 42.7%, 30.8%, and 18.5% for the normal functional group, mild, moderate, and severe renal impairment groups, respectively.

Figure 28. Median Plasma Nirmatrelvir Concentration-Time Plot, Following a Single Oral Dose of Nirmatrelvir/Ritonavir, Linear Scale



Source: Study 1011.

Table 88. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters -Study 1011

Parameter	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n[a,b]	10, 10	8, 8	8, 6	8, 7
AUC_{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC_{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C12 (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C24 (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C_{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
$t_{1/2}$ (hr)	7.725 ± 1.8234	6.606 ± 1.5344	9.948 ± 3.4171	13.37 ± 3.3225
T_{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
VZ/F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CLr (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

Source: Study 1011.
Note: Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for t1/2.
[a.] N1 = Number of participants contributing to the summary statistics.
[b.] n = Number of participants contr buting to the summary statistics for t1/2, AUC_{inf}, CL/F and VZ/F.
Abbreviations: Ae, amount of unchanged drug excreted in urine; AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; C12, 12-hour postdose plasma concentration; C24, 24-hour postdose plasma concentration; CL/F, apparent clearance; CLr, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, total number of participants in the cohort in the indicated population; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 89. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1011

Parameter	Renal Impairment (n=8/group)	Test	Reference	Ratio	90% CI
C_{max} (ng/mL)	Mild	2077	1600	1.29	(1.02,1.65)
	Moderate	2210	1600	1.38	(1.13, 1.69)
	Severe	2369	1600	1.48	(1.11, 1.97)
AUC_{inf} (ng.hr/mL)	Mild	17910	14460	1.24	(0.99, 1.54)
	Moderate	27110	14460	1.87	(1.49, 2.36)
	Severe	44040	14460	3.04	(2.38, 3.90)

Source: Study 1011.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; n, number of subjects in sample; PK, pharmacokinetic

There was an imbalance in safety findings between subjects with severe renal impairment and subjects with normal to moderate renal impairment, with one of the eight subjects with severe renal impairment developing a serious adverse event of moderate acute kidney injury the day after receiving nirmatrelvir (see Section 8.1.2). While it is unclear if these safety findings were related to nirmatrelvir receipt or to the increased comorbidities generally associated with severe renal impairment, this finding raises safety concerns about nirmatrelvir/ritonavir dosing in patients with severe renal impairment (as the therapeutic dose would be higher than 100 mg nirmatrelvir administered with ritonavir).

Study 1028 is an ongoing safety and pharmacokinetic study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in patients with severe renal impairment (for both patients requiring and not requiring hemodialysis). This study is evaluating a PAXLOVID dose of 300 mg nirmatrelvir/100mg ritonavir on Day 1 followed by 150 mg nirmatrelvir/100 mg ritonavir daily on Days 2 to 5 of treatment in subjects with severe renal impairment, which was determined based on population PK modeling and the relative change in CL resulting from renal

impairment from study 1011. Data from this study will inform the appropriate dosing regimen in patients with severe renal impairment.

Hepatic Impairment

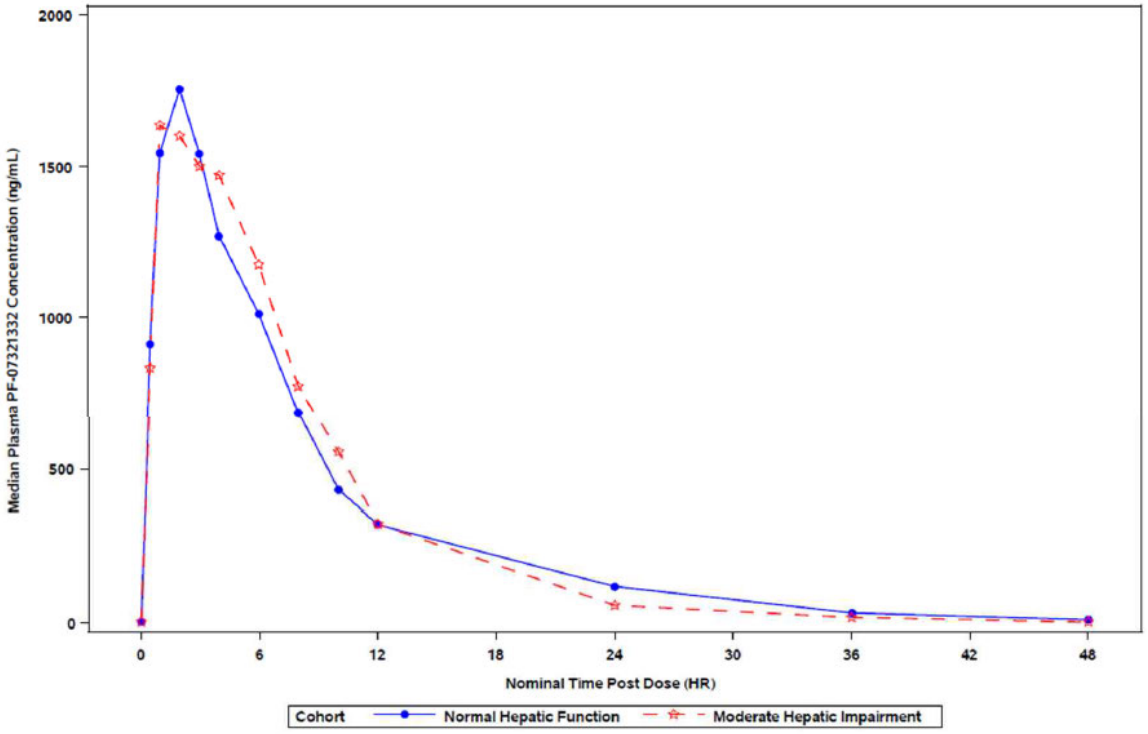
In study 1010, the PK of nirmatrelvir and ritonavir was evaluated in the fasted state in 8 subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9)] and 8 matched controls with normal hepatic function. All subjects received a single 100 mg dose of nirmatrelvir (as an early 100 mg tablet formulation) administered orally in combination with ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to nirmatrelvir dosing.

Blood samples were collected for plasma PK assessment of nirmatrelvir and ritonavir pre-dose through 12 hours on Day 1, at 24 and 36 hours on Day 2, 48 hours on Day 3 and at early termination (if before 48 hours post-dose for nirmatrelvir), if needed. Urine samples were collected at intervals of 0-24 hours after nirmatrelvir dosing on Day 1.

Only total drug concentrations were reported for nirmatrelvir and ritonavir. A description and analysis of nirmatrelvir PK in terms of total concentrations was sufficient for nirmatrelvir since it is not extensively bound to plasma proteins. Despite the increase in ritonavir exposures (as described in next paragraph), nirmatrelvir systemic exposure was nearly identical between the normal hepatic function group and the moderate hepatic impairment group (See Figure 29, Table 90 and Table 91).

Ritonavir systemic exposure following the second dose was higher in subjects with moderate hepatic impairment compared to those with normal hepatic function. Geometric mean ritonavir AUC_{12} and C_{max} in subjects with moderate hepatic impairment was approximately 1.68- and 1.84-fold higher compared to those with normal hepatic function, respectively (See Figure 30 and Table 92). These results are consistent with those of previous studies which showed an AUC_{12} increase of approximately 50 to 60% in moderate hepatic impairment (matched healthy control subjects and cirrhotic patients (matched to a control group of HIV-infected patients with normal liver function test results and without history of HCV or HBV co-infection) receiving the 100mg booster dose in combination with a protease inhibitor, respectively (Seminari et al. 2007; Sekar et al. 2010). It should be noted that these results are based on total concentrations and ritonavir is highly bound to plasma proteins (98-99%). No significant laboratory trends or clinically relevant changes in vital signs were observed in study 1010 after single dose of nirmatrelvir pharmacokinetically enhanced by 100 mg ritonavir. Similarly, the current ritonavir and boosted protease inhibitor labels do not recommend a dose adjustment for mild or moderate hepatic impairment and contribute additional safety data for the use of ritonavir in COVID-19 patients with mild or moderate hepatic impairment. PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) as no PK or safety data regarding the use of nirmatrelvir or ritonavir are available in this population.

Figure 29. Median Plasma Nirmatrelvir Concentration-Time Profiles Following a Single 100 mg Oral Dose of Nirmatrelvir Co-Administered With Ritonavir



Source: Study 1010.

Table 90. Descriptive Summary of Plasma and Urine Nirmatrelvir PK Parameters, Study 1010

Parameter (Unit)	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)
AUC_{inf} (ug.hr/mL)	15.24 (36)	15.06 (43)
AUC_{last} (ug.hr/mL)	14.97 (36)	14.86 (43)
CL/F (L/hr)	6.560 (36)	6.650 (43)
C_{max} (ug/mL)	1.886 (20)	1.923 (48)
$t_{1/2}$ (hr)	7.209 ± 2.0990	5.448 ± 1.5743
T_{max} (hr)	2.000 (0.550 - 2.08)	1.500 (1.00 - 2.00)
VZ/F (L)	65.51 (39)	50.37 (40)
Ae24 (mg)	35.66 (31)	54.23 (23)
CLr (L/hr)	2.509 (46)	3.738 (49)

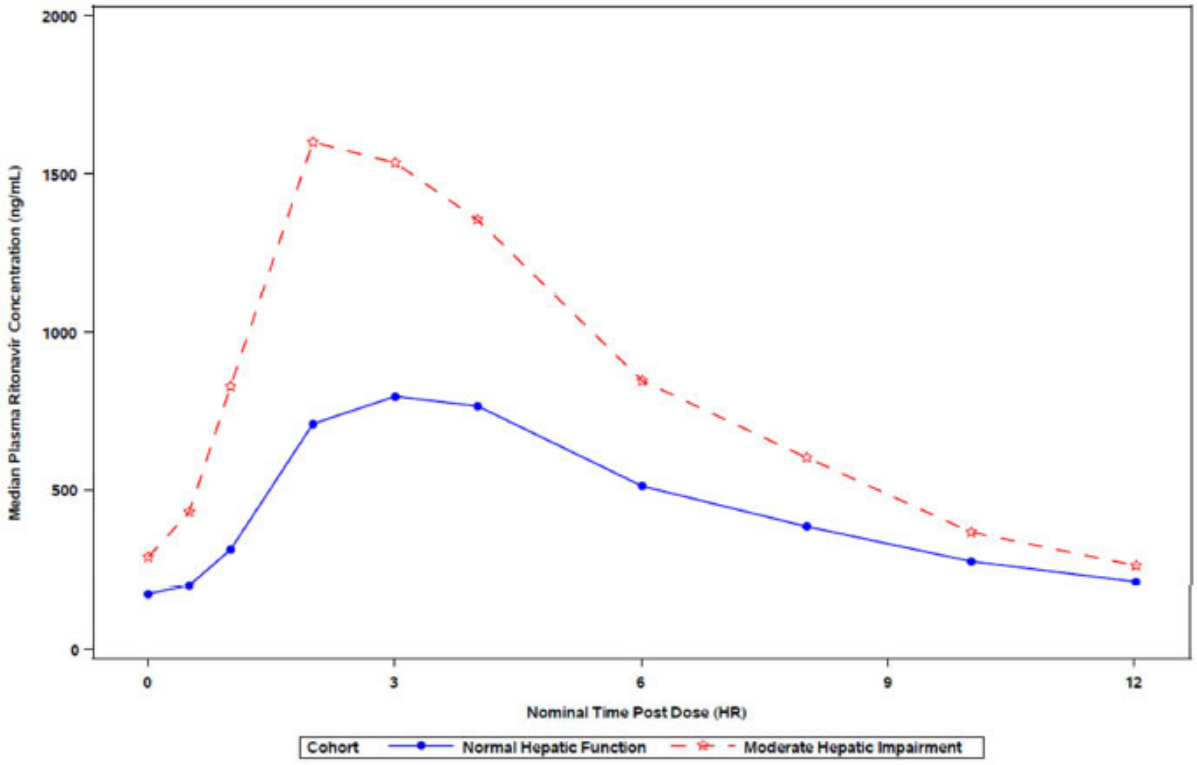
Source: Study 1010.
Note: Geometric Mean (Geometric %CV) for all: except Median (Range) for T_{max} and Arithmetic Mean ± SD for t1/2.
Abbreviations: Ae24, amount of unchanged drug excreted in urine at 24 hours; AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; CLr, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, total number of subjects; PK, pharmacokinetic; SD, standard deviation; t1/2, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 91. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1010

Nirmatrelvir PK Parameter	Moderate Hepatic Impairment	Normal Hepatic Function	Ratio	90% CI
AUC_{inf} (ug.hr/mL)	15.06	15.24	0.99	(0.71,1.38)
C_{max} (ug/mL)	1.92	1.89	1.02	(0.74, 1.40)

Source: Study 1010.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Figure 30. Median Plasma Ritonavir Concentration-Time Profiles Following Second Dose of Ritonavir, Study 1010



Source: Study 1010

Table 92. Descriptive Summary of Plasma Ritonavir PK Parameters, Study 1010

Parameter (Unit)	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)
AUC_{12} (ug.hr/mL)	5.912 (57)	9.929 (36)
C_{max} (ug/mL)	0.8768 (50)	1.611 (42)
T_{max} (hr)	3.000 (2.00 - 4.00)	2.000 (1.00 - 4.00)

Source: Study 1010.
Note: Geometric Mean (Geometric %CV) for all: except Median (Range) for T_{max}.
Abbreviations: AUC_{12}, area under the concentration-time curve to 12 hours; CI, confidence interval; C_{max}, maximum plasma concentration; N, number of total subjects; PK, pharmacokinetic; T_{max}, time for drug to reach maximum concentration

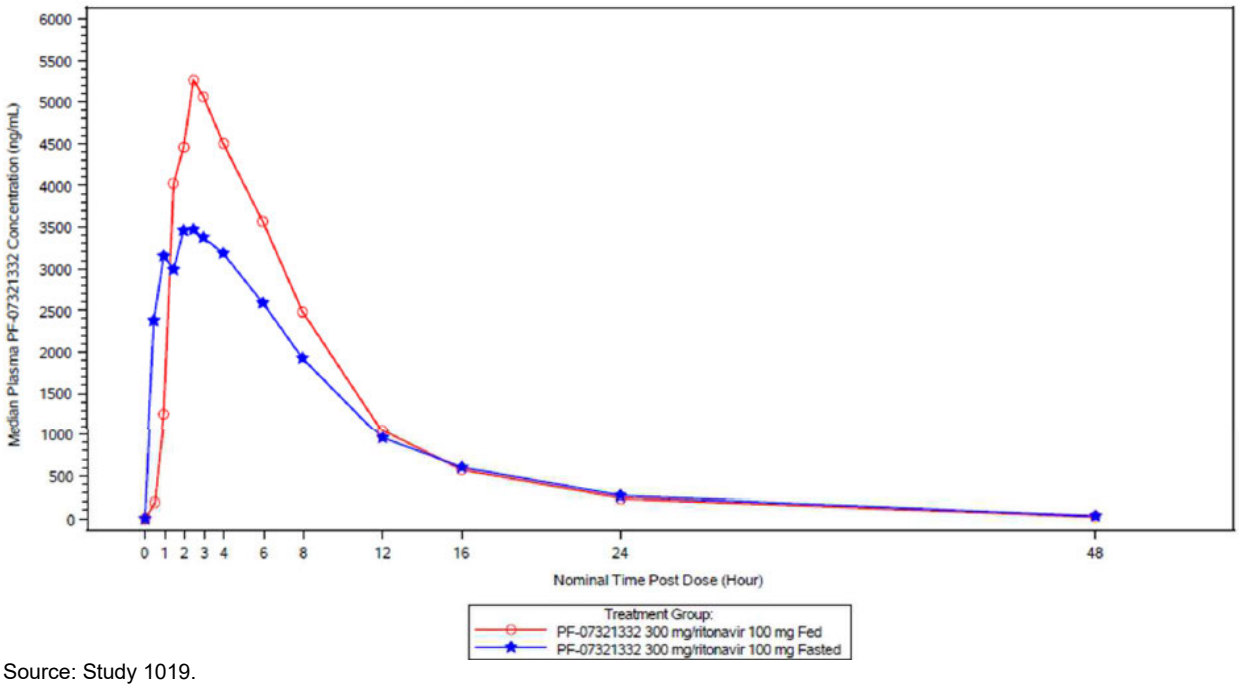
Food Effect Assessment with Commercial Tablet Formulation

The effect of a high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir was evaluated in 24 healthy adults in Study 1019. The study consisted of 2 treatments: a single oral dose of nirmatrelvir 300 mg (2x 150 mg tablets) under fasted conditions and 3 doses of

ritonavir 100 mg at -12-hour, 0 hour and 12 hour relative to nirmatrelvir dosing (Treatment A; n = 12), and a single oral dose of nirmatrelvir 300 mg (2 × 150 mg tablets) under fed conditions with 3 doses of ritonavir 100 mg at -12 hour, 0 hour and 12 hour relative to nirmatrelvir dosing (Treatment B; n=12). Subjects in Treatment B consumed a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast over a 20-minute interval with nirmatrelvir/ritonavir administered within 10 minutes of completion of the meal.

Blood samples were collected through 48 hours post dose for measurement of nirmatrelvir plasma concentrations. Overall, there was an increase in the systemic exposure of nirmatrelvir under fed conditions, with geometric mean values of approximately 20% higher nirmatrelvir AUC and 61% higher C_{max}. See Figure 31 and Table 93. The nirmatrelvir exposures changes in this study are higher than those noted in Study 1001, where coadministration of a nirmatrelvir suspension boosted with ritonavir resulted in 1.5% increase in AUC and 15% increase in C_{max} of nirmatrelvir. In addition, all subjects in the Phase 2/3 pivotal study, EPIC-HR, were dosed without regard to food based on the preliminary food effect results in the first in human study 1001. This was also the basis for the recommendation to take PAXLOVID without regard to food under the EUA, since the dedicated food effect study with the commercial formulation had not yet been conducted. Given nirmatrelvir/ritonavir demonstrated efficacy and was generally well tolerated in the pivotal Phase 2/3 study, PAXLOVID can be dosed without regard to food.

Figure 31. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Nirmatrelvir/Ritonavir Administration Under Fed or Fasted Conditions



Source: Study 1019.

Table 93. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1019

Parameter (unit)	Nirmatrelvir 300mg/ritonavir 100mg Fed (Test)	Nirmatrelvir 300 mg/ritonavir 100 mg Fasted (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	44050	36810	1.20	(1.09, 1.32)
C_{max} (ng/mL)	5951	3696	1.61	(1.39, 1.86)

Source: Study 1019.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Effect of Itraconazole on Nirmatrelvir/Ritonavir

Study 1015 evaluated the PK of nirmatrelvir and ritonavir in eleven healthy adults with and without itraconazole (CYP3A and P-gp inhibitor) coadministration.

Subjects received the oral treatments described below.

Period 1

- Nirmatrelvir/ritonavir 300/100 mg administered orally q12h for a total of 5 doses, from Day 1 morning to Day 3 morning.

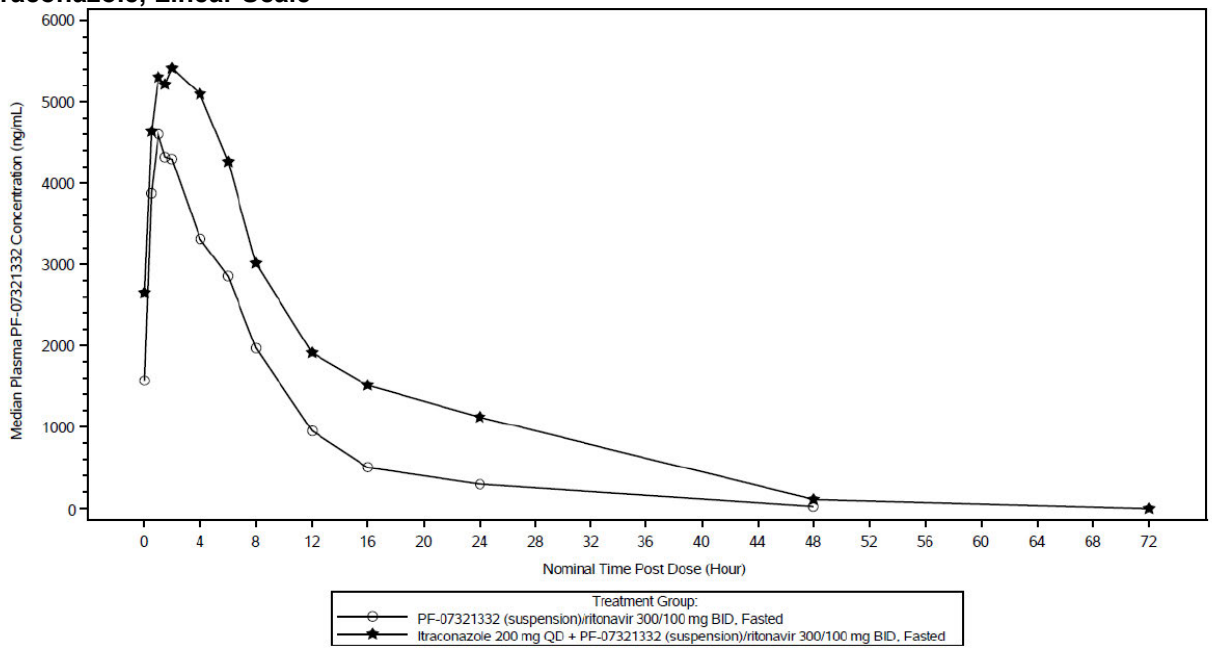
Period 2

- Itraconazole 200 mg orally once daily (using oral solution) from Days 1 through 8; and nirmatrelvir/ritonavir 300/100 mg administered orally q12h from Days 4 through 6, for a total of 5 doses, starting with the first dose on the morning of Period 2, Day 4 and the last dose administered on the morning of Period 2, Day 6.

For measurement of nirmatrelvir and ritonavir concentrations, intensive blood samples were collected at pre-dose and up to 48 hours post dose following the fifth dose on Day 3 of Period 1 and up to 72 hours post the fifth dose in Period 2.

In the presence versus absence of itraconazole, geometric mean nirmatrelvir AUCtau was increased 39% and C_{max} increased 19% (Figure 32, Table 94 and Table 95).

Figure 32. Median Plasma Nirmatrelvir Concentration-Time Profiles Following Multiple Oral BID Doses of Nirmatrelvir/Ritonavir Combination, Administered Alone or With Multiple QD Doses of Itraconazole, Linear Scale



Source: Study 1015.
Abbreviations: BID, twice daily; QD, once per day

Table 94. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Study 1015

Parameter (Unit)	Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)	Itraconazole 200 mg QD + Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)
N1, n[a,b]	11, 11	11, 10
AUC_{last} (ng.hr/mL)	41840 (21)	74430 (21)
AUC_{tau} (ng.hr/mL)	33350 (20)	46290 (18)
CL/F (L/hr)	8.990 (20)	6.478 (18)
C_{max} (ng/mL)	4678 (17)	5546 (15)
$t_{1/2}$ (hr)	8.255 ± 1.9465	7.793 ± 0.89019
T_{max} (hr)	1.020 (0.500 - 2.08)	1.700 (0.500 - 4.00)
VZ/F (L)	104.7 (33)	72.07 (16)

Source: Study 1015.
Note: Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
[a.] N1 = Number of participants contributing to the summary statistics.
[b.] n = Number of participants contr buting to the summary statistics for $t_{1/2}$ and VZ/F.
Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; AUC_{tau}, area under concentration-time curve over dosing interval; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; QD, once per day; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 95. Statistical Summary of Plasma Nirmatrelvir PK Parameters, Study 1015

Parameter	Itraconazole 200 mg QD + nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (Test)	Nirmatrelvir (suspension)/ritonavir 300/100 mg BID, Fasted (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{tau} (ng.hr/mL)	46292	33346	1.39	(1.29,1.49)
C_{max} (ng/mL)	5546.1	4677.5	1.19	(1.13, 1.25)

Source: Study 1015.
Note: Natural log-transformed AUC_{tau} and C_{max} for PF-07321332 were analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratios (and 90% CIs) were expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; QD, once per day

Effect of Carbamazepine on Nirmatrelvir/Ritonavir

Study 1014 evaluated the PK of nirmatrelvir and ritonavir in twelve healthy adults with and without carbamazepine (a strong CYP3A inducer) coadministration.

Participants received the oral treatments described below.

Period 1

- Nirmatrelvir 300 mg (as two 150-mg tablets), administered orally with ritonavir 100 mg (as one 100-mg tablet) as a single dose on Day 1 following an overnight fast.

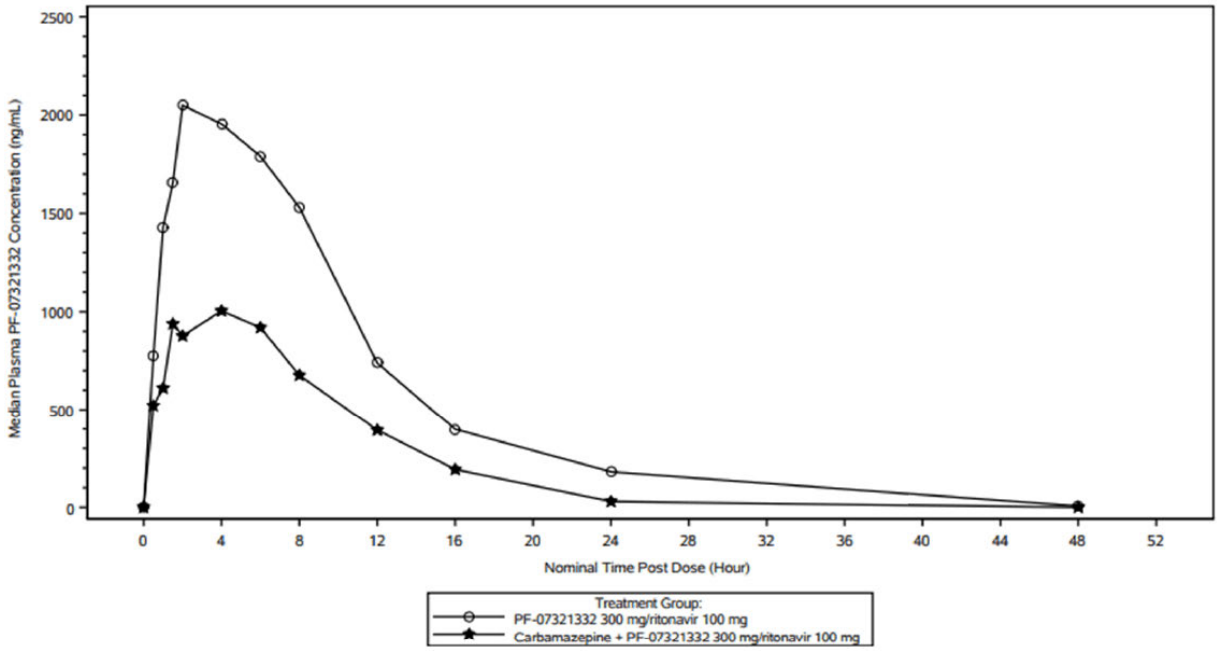
Period 2

- Carbamazepine 100 mg BID administered orally on Days 1, 2, and 3, and titrated up to 200 mg BID on Days 4, 5, 6, and 7. Carbamazepine was eventually titrated up to and maintained at 300 mg BID stably in the rest of Period 2 from Days 8 to 15. Carbamazepine was administered with or without food on all study days except on Study Day 14 when dosing was under fasting conditions. Approximately 15 to 30 min after the carbamazepine dose, on Period 2 Day 14, participants received a single dose of nirmatrelvir 300 mg (as two 150-mg tablets), administered orally with ritonavir 100 mg (as one 100-mg tablet).

For measurement of nirmatrelvir and ritonavir concentrations, intensive blood samples were collected at pre-dose and up to 48 hours post dose post-dose in Period 1, and at Day 14 pre-dose, and at up to 48 hours post-dose in Period 2.

Coadministration of multiple oral doses of carbamazepine titrated up to 300 mg BID decreased single dose nirmatrelvir AUC_{inf} and C_{max} by approximately 55% and 43%, respectively (Figure 33, Table 96 and Table 97). Carbamazepine titrated up to 300 mg BID decreased single dose ritonavir AUC_{inf} and C_{max} by approximately 83% and 74%, respectively (Figure 34, Table 98, and Table 99).

Figure 33. Median Plasma Nirmatrelvir Concentration-Time Profiles Following a Single Oral Dose of Nirmatrelvir/Ritonavir Administered Alone or With Multiple Oral Doses of Carbamazepine, Linear Scale



Source: Study 1014.

Table 96. Descriptive Summary of Plasma Nirmatrelvir PK Parameters, Study 1014

Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
N2, N3[a,b]	12, 12	10, 10
AUC_{inf} (ng.hr/mL)	23010 (23)	10280 (58)
AUC_{last} (ng.hr/mL)	22450 (23)	10050 (58)
CL/F (L/hr)	13.06 (23)	29.17 (58)
C_{max} (ng/mL)	2210 (33)	1300 (43)
$t_{1/2}$ (hr)	6.053 ± 1.7939	3.845 ± 0.99642
T_{max} (hr)	3.00 (1.02-6.00)	1.50 (0.500-4.00)
VZ/F (L)	109.4 (38)	157.2 (69)

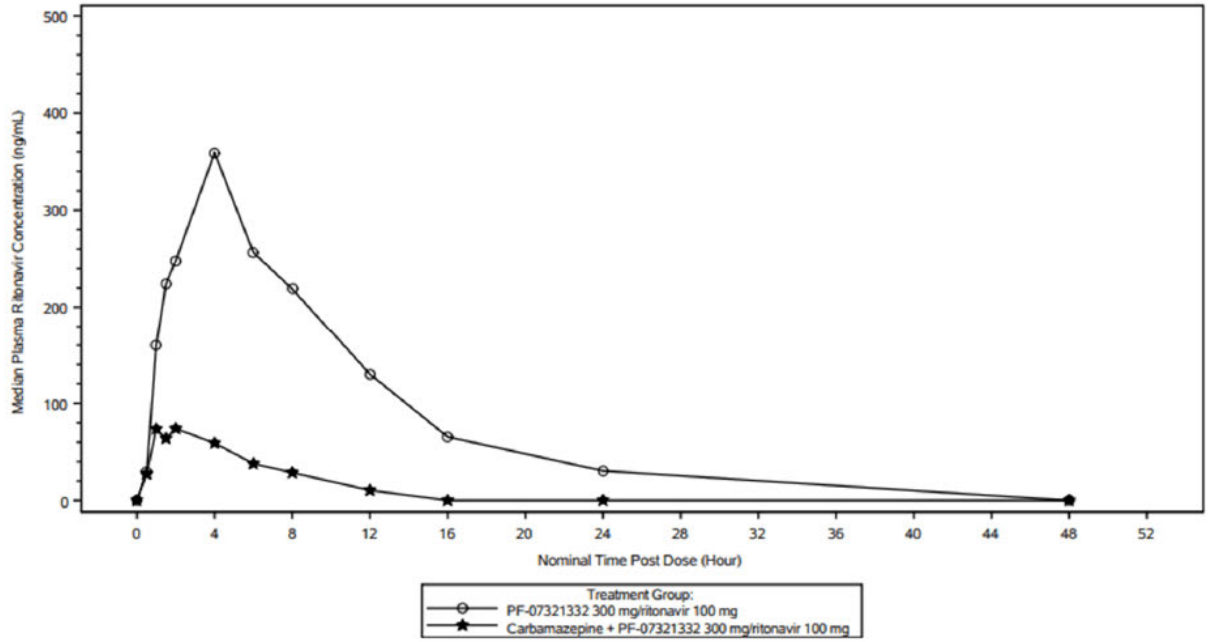
Source: Study 1014.
Note: Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
[a,] N2 = Number of participants contributing to the summary statistics
[b.] N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and VZ/F.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{tau}, area under concentration-time curve over dosing interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 97. Statistical Summary of Nirmatrelvir PK Parameters, Study 1014

Parameter (unit)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (Test)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	10240	23010	0.45	(0.34, 0.59)
AUC_{last} (ng.hr/mL)	10010	22450	0.45	(0.34, 0.59)
C_{max} (ng/mL)	1256	2210	0.57	(0.47, 0.69)

Source: Study 1014.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for PF-07321332 are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Figure 34. Median Plasma Ritonavir Concentration-Time Profiles Following a Single Oral Dose of Nirmatrelvir/Ritonavir Administered Alone or With Multiple Oral Doses of Carbamazepine, Linear Scale



Source: Study 1014.

Table 98. Descriptive Summary of Plasma Ritonavir PK Parameters, Study 1014

Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
N2, N3[a,b]	12, 12	10, 8
AUC_{inf} (ng.hr/mL)	3599 (47)	677.6 (61)
AUC_{last} (ng.hr/mL)	3414 (47)	466.2 (104)
CL/F (L/hr)	27.78 (48)	147.6 (61)
C_{max} (ng/mL)	359.3 (46)	96.07 (71)

Parameter (unit)	Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (N=12)
$t_{1/2}$ (hr)	6.149 ± 2.2413	3.345 ± 0.79964
T_{max} (hr)	3.98 (1.48-4.20)	1.98 (0.983-4.00)
VZ/F (L)	234.0 (36)	697.5 (51)

Source: Study 1014.
[a.] N2 = Number of participants contributing to the summary statistics
[b.] N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and VZ/F.
Note: Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, total number of participants in the treatment group in the indicated population; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time for drug to reach maximum concentration; VZ/F, apparent volume of distribution

Table 99. Statistical Summary of Ritonavir PK Parameters, Study 1014

Parameter (unit)	Carbamazepine + Nirmatrelvir 300 mg/ Ritonavir 100 mg (Test)	Nirmatrelvir 300mg/ Ritonavir 100 mg (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
AUC_{inf} (ng.hr/mL)	596.4	3599	0.17	(0.13, 0.20)
AUC_{last} (ng.hr/mL)	441.1	3414	0.13	(0.09, 0.18)
C_{max} (ng/mL)	91.94	359.3	0.25	(0.19, 0.35)

Source: Study 1014.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for PF-07321332 are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Effect of Nirmatrelvir/Ritonavir and Ritonavir on Dabigatran

Study 1012 evaluated the effect of nirmatrelvir/ritonavir and ritonavir on the PK of dabigatran (a P-gp substrate) in 24 healthy participants. Each participant received three treatments, each followed by a 3-day washout period.

Treatment 1

- Dabigatran 75 mg as a single oral dose.

Treatment 2

- Nirmatrelvir/ritonavir 300 mg/100 mg q12hours as a multiple oral dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran was administered orally as a single dose.

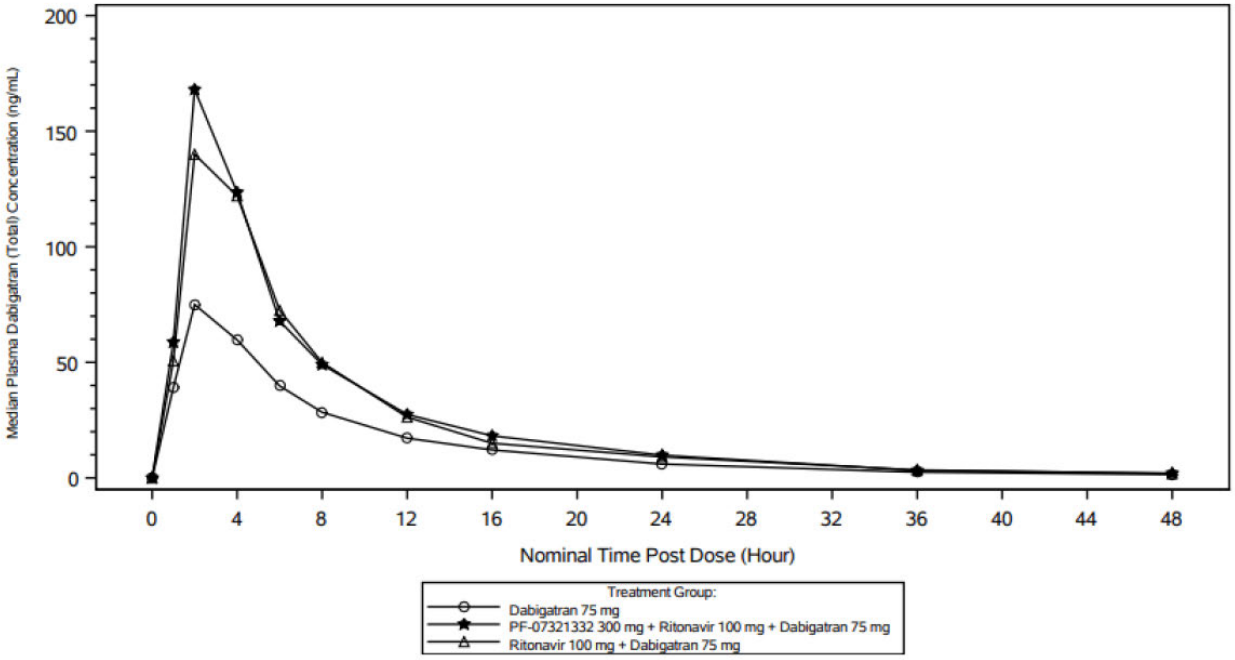
Treatment 3

- Ritonavir 100 mg q12h as a multiple oral dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran was administered orally as a single dose.

Blood samples were collected pre-dose and up to 48 hours post-dose in each treatment group for PK assessments of nirmatrelvir, ritonavir and dabigatran.

The percent ratio of geometric means (90% CI) for dabigatran AUC_{inf} and C_{max} were 1.94 (1.55, 2.44) and 2.33 (1.72, 3.16) respectively, following dabigatran administration with multiple doses of nirmatrelvir/ritonavir combination as compared to administration alone (Figure 35 and Table 100).

Figure 35. Median Plasma Dabigatran Concentration-Time Profiles Following A Single Oral Dose Administered Alone and in Combination With Multiple Oral Doses of Nirmatrelvir/Ritonavir or Ritonavir



Source: Study 1012.

Table 100. Statistical Summary of Plasma Dabigatran PK Parameters, Study 1012

Parameter (Unit)	Test	Reference	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
Nirmatrelvir 300 mg + Ritonavir 100mg + Dabigatran 75 mg vs. Dabigatran 75 mg				
AUC_{inf} (ng.hr/mL)	1221	627.9	1.94	(1.55, 2.44)
AUC_{last} (ng.hr/mL)	1201	558.3	2.15	(1.60, 2.90)
C_{max} (ng/mL)	158.3	67.91	2.33	(1.72, 3.16)
Ritonavir 100mg + Dabigatran 75 mg vs. Dabigatran 75 mg				
AUC_{inf} (ng.hr/mL)	1062	627.9	1.69	(1.35, 2.11)
AUC_{last} (ng.hr/mL)	893.5	558.3	1.60	(1.19, 2.15)
C_{max} (ng/mL)	116.7	67.91	1.72	(1.28, 2.32)

Source: Study 1012.
Note: Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for Dabigatran are analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Reduced dataset excluded profiles where all concentrations were BLQ and C_{max} and AUC_{last}
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; BLQ, below limit of quantitation; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

Effect of Nirmatrelvir/Ritonavir and Ritonavir on Midazolam

Study 1013 evaluated the effect of nirmatrelvir/ritonavir and ritonavir on the PK of midazolam (a CYP3A4 substrate) in 10 healthy subjects. Each subject received the treatments in the fasted state as described below.

Treatment A

- Single oral dose of 2 mg midazolam followed by a 2-day washout period.

Treatment B

- One hundred mg nirmatrelvir/100 mg ritonavir, administered orally, every 12 hours for 9 doses, with the last dose administered on the morning of Day 5. On Day 5, the nirmatrelvir/ritonavir dose was co-administered with a single oral dose of midazolam 2 mg followed by a 7-day washout period.

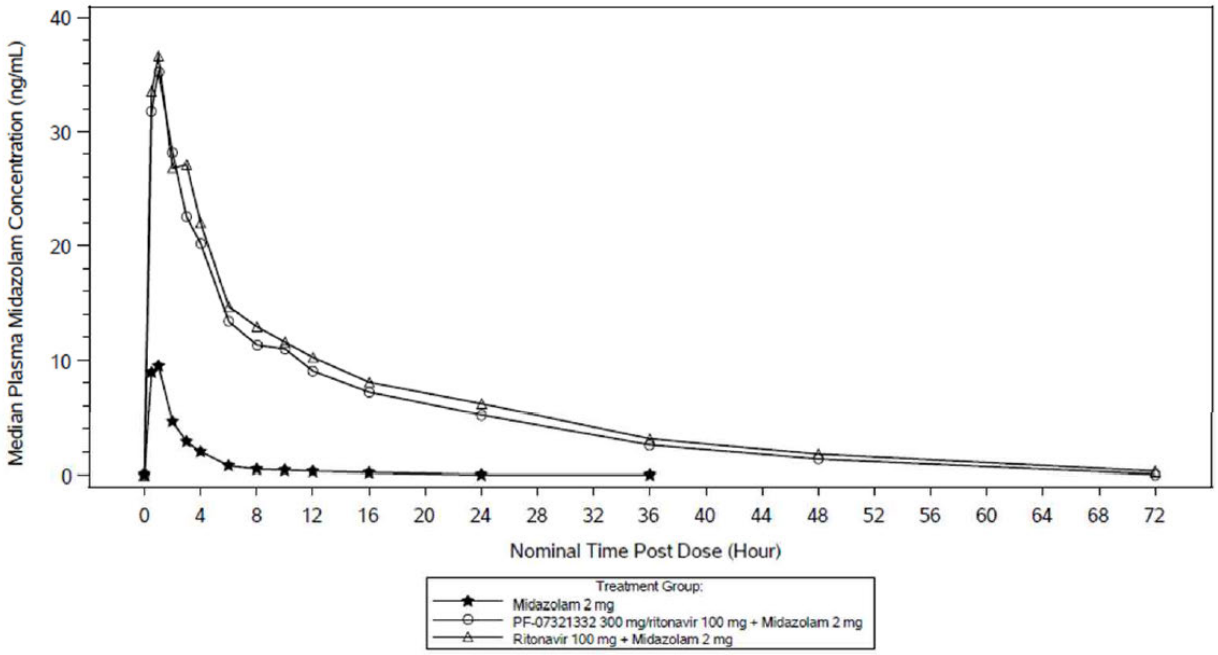
Treatment C

- One hundred mg ritonavir, administered orally, every 12 hours thereafter for a total of 9 doses, with the last dose administered on the morning of Day 5. On Day 5, the ritonavir dose was co-administered with a single oral dose of midazolam 2 mg followed by a 7-day washout period.

Blood samples were collected pre-dose and up to 36 hours post-dose for midazolam concentrations in Treatment group A and up to 72 hours post-dose for nirmatrelvir, ritonavir and midazolam concentrations in Treatment groups B and C.

The percent ratio of the geometric mean (90% CI) for midazolam AUC_{inf} and C_{max} were 14.30 (12.04, 17.00) and 3.68 (3.19, 4.25) respectively, following midazolam administration with multiple doses of nirmatrelvir/ritonavir as compared to administration alone (Figure 36 and Table 101).

Figure 36. Median Plasma Midazolam Concentration-Time Profiles Following A Single Oral Dose Administered Alone and in Combination With Multiple Oral Doses of Nirmatrelvir/Ritonavir or Ritonavir



Source: Study 1013

Table 101. Statistical Summary of Plasma Midazolam PK Parameters, Study 1013

Parameter (Unit)	Test	Reference	Ratio (Test/Reference) of Adjusted Geometric Means	90% CI of Ratio
Nirmatrelvir 300 mg/Ritonavir 100mg + Midazolam 2 mg vs. Midazolam 2 mg				
AUC_{inf} (ng.hr/mL)	362.5	25.35	14.30	(12.04, 17.00)
AUC_{last} (ng.hr/mL)	353.4	24.35	14.51	(12.24, 17.21)
C_{max} (ng/mL)	36.29	9.852	3.68	(3.19, 4.25)
Ritonavir 100mg + Midazolam 2 mg vs. Midazolam 2 mg				
AUC_{inf} (ng.hr/mL)	417.1	25.35	16.45	(13.86, 19.53)
AUC_{last} (ng.hr/mL)	408.3	24.35	16.77	(14.14, 19.89)
C_{max} (ng/mL)	38.15	9.852	3.87	(3.35, 4.47)

Source: Study 1013.
Note: Natural log-transformed AUCinf, AUC_{last} and C_{max} for Midazolam are analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within sequence as a random effect.
Note: The ratio (and 90% CIs) are expressed as percentages.
Note: Values in table are the adjusted geometric means.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic

14.3. Bioanalytical Method Validation and Performance

Bioanalytical methods used to measure nirmatrelvir and ritonavir concentrations in human plasma, urine and dried blood were fully validated and met precision and accuracy acceptance criteria (±15%, ±20% at the lower limit of quantification (LLOQ), see Table 102).

Method C4679002 supported the Pivotal Phase 2/3 Study 1005 (Table 102). Validated bioanalytical methods used in the clinical drug-drug interaction (DDI) studies also met precision and accuracy acceptance criteria and are summarized in Table 103.

Table 102. Bioanalytical Methods Used to Quantify Nirmatrelvir and Ritonavir in Plasma, Urine, and Dried Blood

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/ Anticoagulant	Long-Term Stability	Supported Clinical Studies
071459	LC-MS/MS	Nirmatrelvir	10.0-50,000	Human Plasma/K2EDTA	51 days at -20°C and 70°C	1001
C4679002	LC-MS/MS	Nirmatrelvir and Ritonavir	Nirmatrelvir: 10.0-10,000 Ritonavir: 5,00-5,000	Human Plasma/K2EDTA	200 days at 20°C and -80°C	1005 1006 1010 1011 1012 1013 1014 1015 1019
074112	LC-MS/MS	Nirmatrelvir	10.0-50,000	Human Urine	63 days at -20°C and -70°C	1001
C4679003	LC-MS/MS	Nirmatrelvir	100-200,000	Human Urine	92 Days 20°C and 80°C	1011 1010
C4679008	LC-MS/MS	Nirmatrelvir and Ritonavir	Nirmatrelvir: 10.0-10,000 Ritonavir: 5,00-5,000	Human Dried Blood/K2EDTA	29 days at -20°C and -80°C	1026

Source: Validation reports 071459, C4679002, 074112, C4679003, C4679008.
Abbreviations: K2EDTA, anticoagulant; LC, liquid chromatography; MS/MS, tandem mass spectrometry

Table 103. Bioanalytical Methods Used in Clinical DDI Studies

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/ Anticoagulant	Long-Term Stability	Supported Clinical Studies
B7459007	HPLC-MS/MS	Total Dabigatran	1.00 - 800	Human Plasma/K2EDTA	95 days at -20°C and -80°C	1012
C4679007	LC-MS/MS	Midazolam	0.100-100	Human Plasma/K2EDTA	63 days at -20°C	1013

Source: Validation report B7459007 and C4679007.
Abbreviations: HPLC, high-performance liquid chromatography; K2EDTA, anticoagulant; LC, liquid chromatography; MS/MS, tandem mass spectrometry

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Review Summary

This review aims to 1) evaluate appropriate treatment duration in immunocompromised patients based on QSP modeling, 2) provide pharmacometrics perspective in support of the dose in the indicated population.

Applicant's quantitative systems pharmacology (QSP) modeling suggests that the treatment duration of 5 days, as indicated in the current EUA fact sheet and proposed label, might not be sufficient for immunocompromised patients. A longer treatment duration might be potentially beneficial to further manage viral RNA shedding in this patient subgroup, thus providing additional support for the need of the ongoing EPIC-IC trial.

The QSP model is designed to include the current mechanistic understanding of the interplay between viral infection/replication and immune response in the absence or presence of antiviral products with calibration/validation using longitudinal data from observational study of biomarkers (e.g., SARS-CoV-2 RNA levels, circulating cytokines/chemokines, and immune cells signature), and aggregate virology data from several randomized control trials of antiviral products. While the calibration with full EPIC-HR data inclusive of immune markers is not currently available, the current version of QSP model aligned with the aggregate virology data and is deemed qualitatively acceptable to depict viral dynamics of SARS-CoV-2 in patients with mild-to-moderate COVID-19 (PAXLOVID-eligible population) in the absence and presence of PAXLOVID.

The immunocompromised (IC) virtual populations were generated from the virtual population representative of the PAXLOVID-eligible population. In combination with QSP model, the proposed immunocompromised virtual populations reproduced the prolonged viral shedding profile and are acceptable to inform the dose proposal in EPIC-IC trial based on the predicted efficacy of viral suppression (Aydillo et al. 2020; Caillard et al. 2021). Even with uncertainty, the QSP analysis suggests that a prolonged treatment duration beyond 5 days may be beneficial for this patient population.

Applicant's population pharmacokinetics (PopPK) model is generally acceptable to characterize nirmatrelvir (NIR) PK profiles in patients with COVID-19 who received multiple doses of PAXLOVID that support the labeling language with regards to intrinsic factors (age, weight, gender, race/ethnicity, renal impairment). Parameters were generally estimated with acceptable precisions. The derived individual exposure metrics is not expected to be credible for exposure-response analyses since ETA shrinkages are moderate to high (>50%). There is no unacceptable bias in goodness-of-fit plots and the prediction corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations.

For dosage in adolescents and severe renal impaired patients, PK matching approach extrapolated with population PK model was employed. The conclusions from modeling perspective were in-line with those drawn from the analysis using the preliminary model documented in the EUA review. The data for model validation are very limited during the current review cycle.

14.5.2. Applicant's QSP Modeling and Analysis

14.5.2.1. Objectives

The primary objectives of Applicant's analysis were to:

- Support EPIC-HR dose selection for intent-to-treat population
- Evaluate an appropriate treatment duration in immunocompromised population from viral suppression perspective

14.5.2.2. Overview of Studies Included in QSP Analysis

The Applicant developed a QSP model to describe SARS-CoV-2 viral dynamics on a population scale and to subsequently use the model to support selection of treatment duration in target population, and specific population such as immunocompromised patients. Clinical data used in calibration of the model parameters are listed in Table 104.

Table 104. Clinical Data Used in QSP Modeling Calibration

Study	Description	Drug and Data Used
Curated data	Observational studies in moderate to severe patients with COVID-19	• Drug: None • Data: Individual viral RNA shedding, cytokine and chemokine, and PBMCs data in mainly hospitalized patients*
Blaze-1	A Phase 3 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	• Drug: Bamlanivimab and etesevimab • Data: Mean viral RNA shedding data and disease severity**
COV-2067	A Phase 1-3 study to assess the safety, tolerability, and efficacy of anti-spike SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory adult and pediatric patients with COVID-19 (only Phase 2/3 data were used)	• Drug: Casirivimab and imdevimab, • Data: Mean viral RNA shedding data and disease severity**
MK-4422	A Phase 2 study to assess the safety, tolerability, and efficacy of molnupiravir to eliminate infectious virus detection in persons with COVID-19	• Drug: Molnupiravir • Data: Mean viral RNA shedding data
EPIC-HR	A Phase 2/3 study to assess the safety and efficacy to PAXLOVID for the treatment of non-hospitalized symptomatic adults with COVID-19.	• Drug: PAXLOVID • Data: Mean viral RNA shedding data

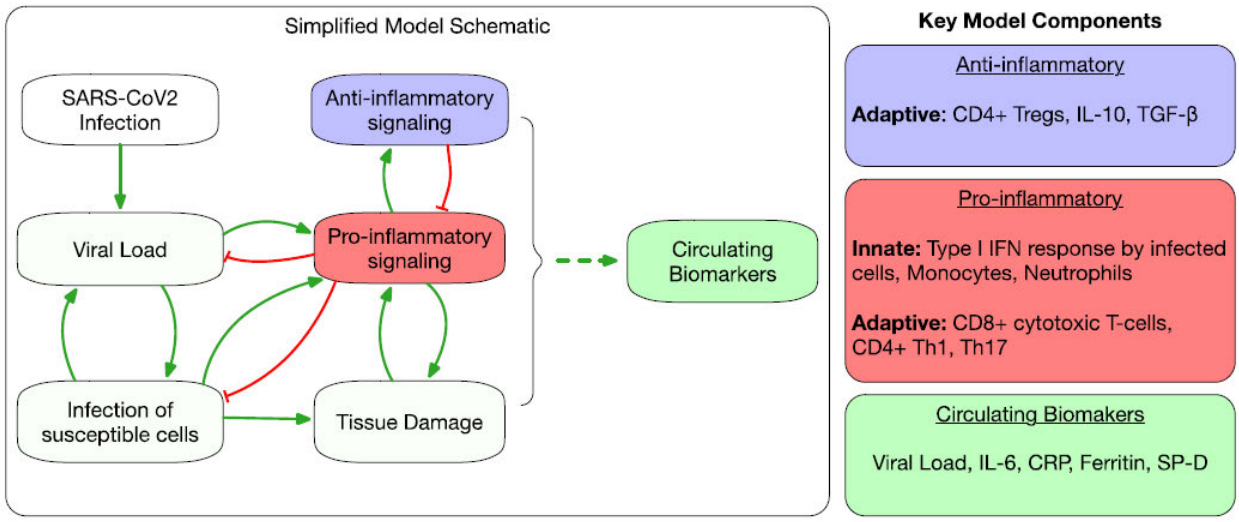
Source: Adapted from Applicant's PK report, Table 1.
* (Lucas et al. 2020; Mann et al. 2020; Mudd et al. 2020; Gastine et al. 2021)
** Plasma IL-6 threshold of 40 pg/mL was used as the primary biomarker for clinical endpoint in the model for disease severity classification.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; IL, interleukin; PBMC, peripheral blood mononuclear cells; QSP, quantitative system pharmacology; RNA, ribonucleic acid

14.5.2.3. QSP model

The QSP modeling and simulation was conducted using MATLAB 2019b.

QSP model leverages existing mechanistic knowledge to describe the disease pathophysiology of viral dynamics and the innate and adaptive immune response with a set of ordinary differential equations (ODEs) in alveolar and plasma compartments (Figure 37). The pharmacodynamic effects of anti-viral products were added to the model according to their mechanism of action.

Figure 37. Simplified Model Schematic



Source: Applicant's EPIC-IC QSP model summary, Figure 1.
Abbreviations: CD, cluster of differentiation; CRP, C-reactive protein; IFN, interferon; IL, interleukin; SP-D, surfactant protein D; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TGF, transforming growth factor; Th, T helper cell

Model parameters were informed by literature and experimental data or calibrated by unit test and/or clinical data. There are over 200 parameters included in the QSP model, the specific breakdown relating to their attributes is as follows:

- Calibrated with unit tests: 140 parameters involved in immune/alveolar cell differentiation, regeneration, maturation, or clearance, immune cell activation by cytokines, and cytokine induced tissue damage
- From literature: 28 parameters describing cell death rate or cytokine clearance, and dynamics of circulating biomarkers
- Calibrated with observational clinical data and randomized control trials: 50 parameters involved in viral infectivity or shedding, death of infected cells, immune cell activation, and basal production of cytokines

14.5.2.4. Virtual Population Development

Twenty-eight parameters in the last category with high sensitivity and uncertainty (Table 105) were selected to form virtual population comprised of sets of parameters which imitate pathophysiological heterogeneity in patient population. The virtual population was generated and refined in a stepwise fashion (Dai et al. 2021; Rao et al. 2023): 1) confining the distribution of parameter sets using various observed markers (e.g., viral RNA shedding, circulating cytokines) from curated observational studies on COVID-19 to obtain a plausible population, and 2) selecting a subset of plausible subjects whose simulated responses conform to interventional data

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from a published randomized control trial (Blaze 1 study) to form a virtual population that represents symptomatic outpatient COVID-19 population (n = 502).

The important assumptions for modeling and simulation are listed below, which are informed by the clinical findings, literatures, or rational premise from analysis standpoint:

1. Symptom onset coincides with the peak viral RNA shedding to translate "day of symptom onset" to "day of infection" for calibration
2. A homogenous initial inoculum of 10 viral RNA copies/mL
3. Endogenous Ab response on Day 20 post infection
4. Innate immune cells behave as log sensors to pathogen levels rather than having saturable maturation kinetics
5. Post peak, virus can no longer infect new susceptible cells within the host when the viral load declines below 10^4 viral RNA copies/mL (10^3 copies/mL threshold investigated in a sensitivity analysis that showed no obvious difference in viral dynamics (Rao et al. 2023)) to avoid unphysiological rebound at later time points when viral RNA is close to the lower limit of quantification for SARS-CoV-2 real-time, reverse transcription-polymerase chain reaction (RT-PCR) assay
6. The effects of nirmatrelvir were only captured as a suppression of net viral production and shedding from infected cells despite of the intracellular life cycle of SARS-CoV-2

The plausible population is composed of subjects exhibiting viral dynamics that are physiologically realistic (Figure 38).

Figure 39 shows the distribution of parameters for the refined virtual population, where the median of the parameters in virtual population in generally aligns with the nominal value. The viral dynamics of this virtual population was validated against viral RNA shedding data of two other published randomize control trials (COV-2067 study, MK-4422 study) which showed good agreement (Rao et al. 2023). The agreement in viral dynamics was also observed for different baseline viral RNA shedding levels (Figure 40).

14.5.2.5. Application of QSP Modeling to Inform Treatment Duration in Target Populations

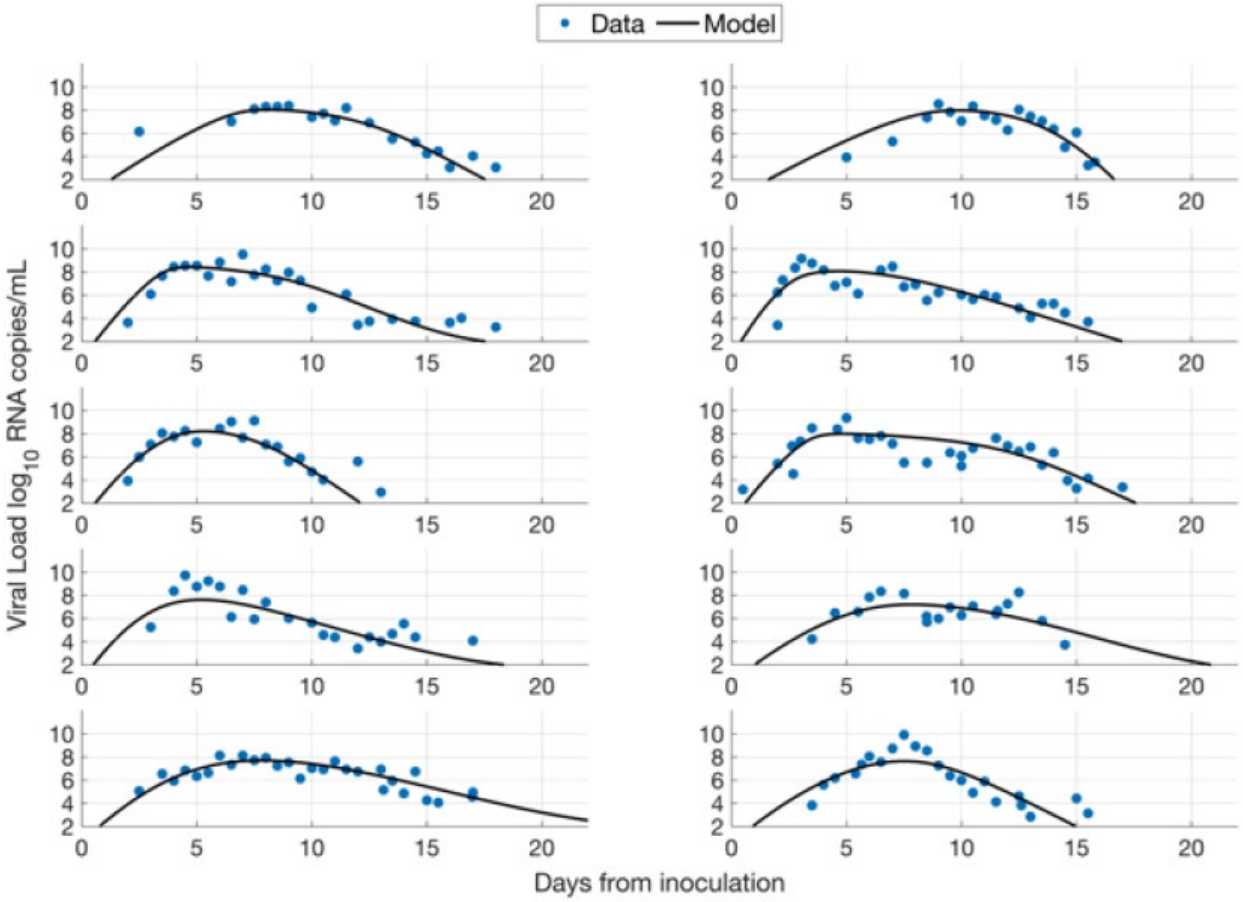
The QSP model together with preliminary population PK model (refer to EUA review for the PK model) were used to inform selection of treatment duration for EPIC-HR. In this model, the E_{max} of the therapeutic is fixed to one, the in vivo potency of nirmatrelvir (EC_{50}) was estimated from preclinical data and subsequently updated to align with the observed experimental virology data for simulating treatment with PAXLOVID. Assuming 4 days post peak viral RNA shedding/symptom onset, the viral dynamics of two dosing durations (i.e., 5-day and 10-day) were assessed. The model predicted that a longer dosing regimen would not provide meaningful difference in viral RNA shedding lowering efficacy at Day 7 or Day 10 regardless of clinical potency (Figure 41).

Table 105. Parameters Varied to Generate Plausible and Virtual Population

Parameter	Description
A_V	viral shedding by infected cells
b_V	endogenous viral clearance
b_I	death rate for infected cells
a_DC	rate constant for production of mature dendritic cells
km_DC_IL10	IC_{50} for inhibition of DC activation by IL-10
a_Th1	rate constant for activation of Th1 cells
a_Th17	rate constant for activation of Th17 cells
a_Treg	rate constant for Treg activation
a_M1	rate constant for activation of macrophages
a_CTL	rate constant for CTL activation
a_ifnb	basal induction of Type I IFN
b_dAT1	death rate for damaged AT1 cells
km_int_IFNb	IC_{50} for anti-viral effects of Type I IFN
k_v	rate constant for viral activation of innate immune cells
k_I	rate constant for innate immune activation by infected cells
k_dAT	rate constant for innate immune activation by damaged cells
k_kill	rate constant for infected cell clearance by $CD8^+$ cell clearance
k_damage_cyt	rate constant overall cytokine damage
k_int	viral endocytosis by AT2
basal_tnfa	basal production rate of TNF
basalil6	basal production rate of IL-6
basalil1	basal production rate of IL-1
basalifng	basal production rate of IFNg
basalifnb	basal production rate of Type I IFN
basalil2	basal production rate of IL-2
basalil12	basal production of IL-12
basalgmcsf	basal production of GM-CSF
basalil10	basal production rate of IL-10

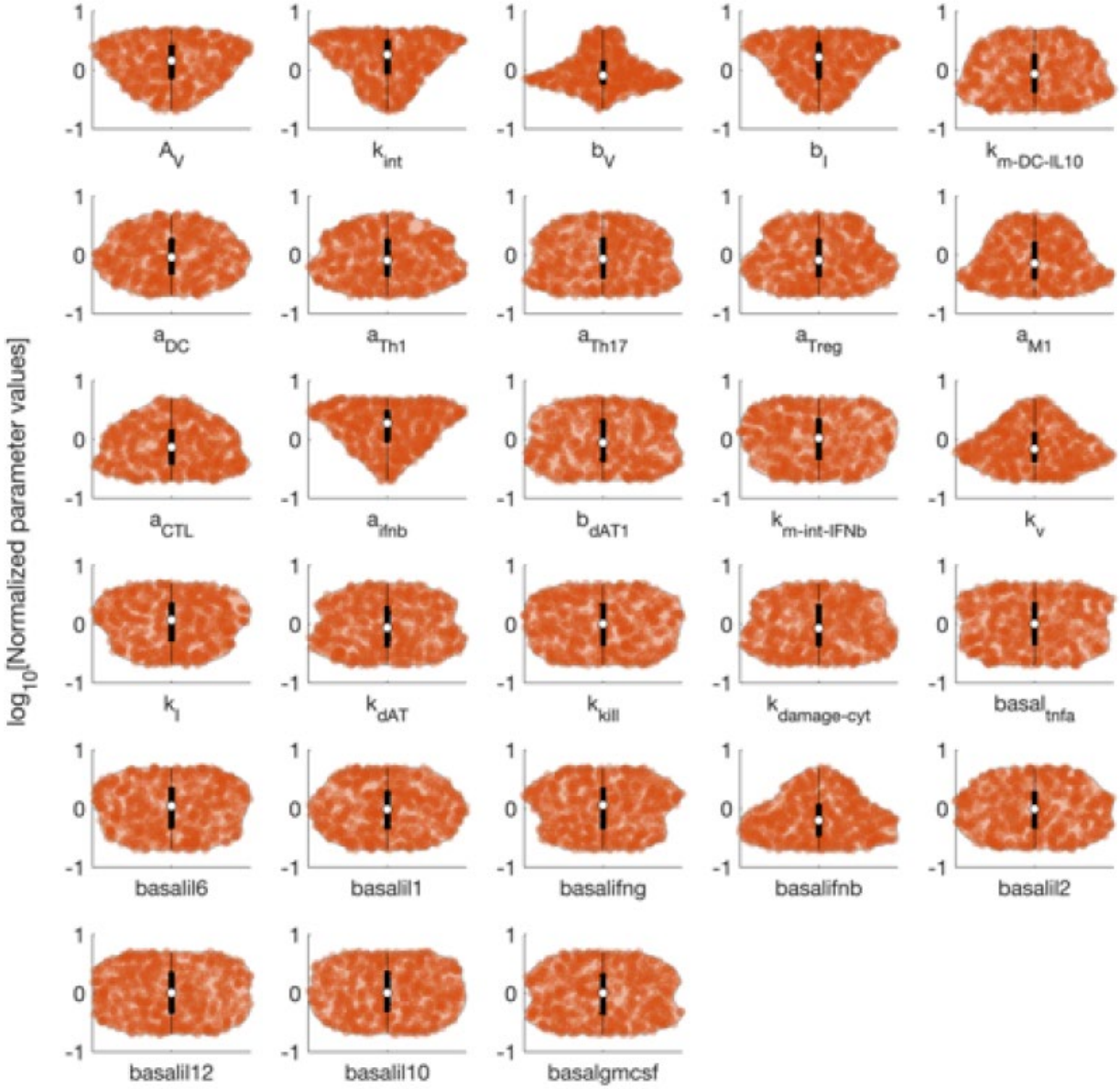
Source: Applicant's EPIC-IC QSP model summary, Appendix 3.
Abbreviations: AT2, angiotensin 2 receptor; CD, cluster of differentiation; CTL, cytotoxic T lymphocytes; DC, dendritic cells; EC_{50}, median effective concentration; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; SP-D, surfactant protein D; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; Th, T helper cell; TNF, tumor necrosis factor

Figure 38. Viral Dynamics in Selected Virtual Subjects From the Plausible Population That Matched Individual Data in a Published SARS-CoV-2 Human Challenge Study



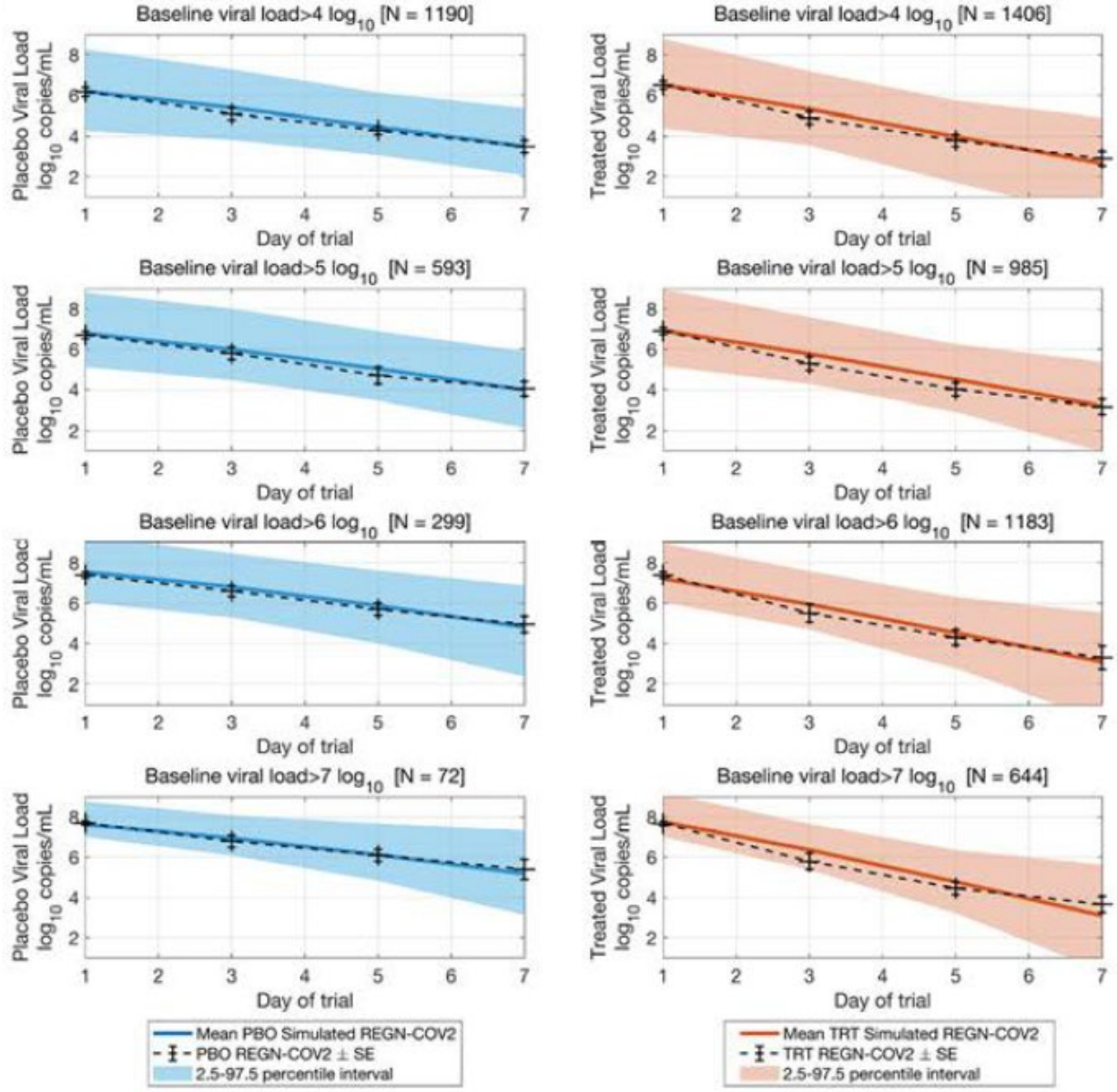
Source: Applicant's EPIC-IC QSP model summary, Figure 3.
Note: Data is extracted for subjects with confirmed symptomatic SARS-CoV-2 Infection with above LOQ PCR assay measurements upon viral inoculation from Killingley et al (Killingley et al. 2022).
Abbreviations: log, logarithm; LOQ, limit of quantification; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; QSP, quantitative systems pharmacology; RNA, r bonucleic acid

Figure 39. Distribution of Parameters for the Virtual Population Matching the Blaze-1 Clinical Data



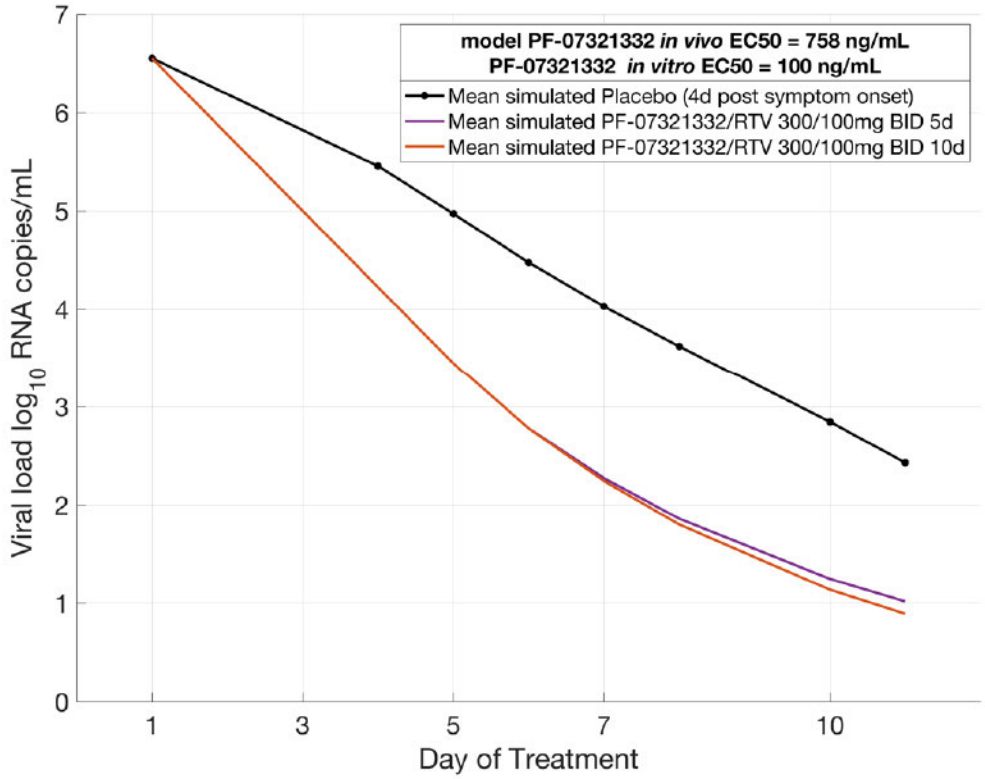
Source: Applicant's EPIC-IC QSP model summary, Figure 2.
Note: Parameters normalized by the nominal value of each parameter.
Abbreviations: log, logarithm; QSP, qualitative systems pharmacology

Figure 40. Viral Dynamics Selected From the Plausible Population Grouped by Baseline Viral Loads That Match the Strata in Subgroup Analysis of Viral Dynamics in REGEN-COV Phase 2 Study



Source: Applicant's EPIC-IC QSP model summary, Figure 4.
Note: Mean viral RNA shedding trajectories for each subgroup is extracted from Weinreich et al (Weinreich et al. 2021). The shaded regions represent the 95% intervals for the simulated viral RNA shedding. The virtual subject was selected from the plaus ble population to match the subgroup by baseline viral RNA shedding.
Note**:** The above virtual populations are obtained by selecting virtual subjects from the plaus ble population to independently match each subgroup in the placebo and treated conditions, therefore representing different virtual populations from those selected from the virtual population calibrated by Blaze 1 (n=502). The graph of the latter virtual population for the purpose of validation in REGEN-COV was reported in Rao R et al.'s paper (Rao et al. 2023).
Abbreviations: log, logarithm; N, total number of subjects; n, number of subjects in sample; QSP, quantitative systems pharmacology; RNA, ribonucleic acid; SE, standard error

Figure 41. QSP Model Predictions for Symptomatic COVID-19 Patients



Source: Applicant's QSP model summary, Figure 2.
Abbreviations: BID, twice daily; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; EC_{50}, median effective concentration; QSP, quantitative systems pharmacology; RNA, ribonucleic acid

Clinical data are not available to calibrate the viral dynamics for Omicron viral variants. According to the reported viral dynamics of Omicron relative to Delta, Applicant stated that the difference is within the variability contained in the plausible and virtual population. The parameter K_int that describes viral infectivity may be sensitive to viral variant, for instance, Omicron is known for a higher infectivity than Delta, the viral RNA shedding could be subsequently shifted, which may impact the observable difference between placebo and treatment.

14.5.2.6. QSP Analysis in Immunocompromised Population

Virtual Population Development for Immunocompromised Patients

QSP model is being calibrated iteratively throughout the development. When EPIC-HR data became available, the Applicant adjusted the parameters of virtual population as well as IC_{50} to match the aggregate virology data (Figure 42). The resulting virtual population is termed the nominal virtual population (n = 739). This nominal virtual population corresponds to the overall PAXLOVID eligible population and was used to generate immunocompromised patients who are expected to mount an inadequate innate and adaptive immune response to SARS-CoV-2 infection. Notably in this nominal virtual population, the model overpredicts the viral RNA shedding at early time points primarily due to an under-representation in virtual population of the proportion of participants that are tested positive for COVID-19 RT-PCR with viral RNA shedding under LLOQ at baseline in EPIC-HR.

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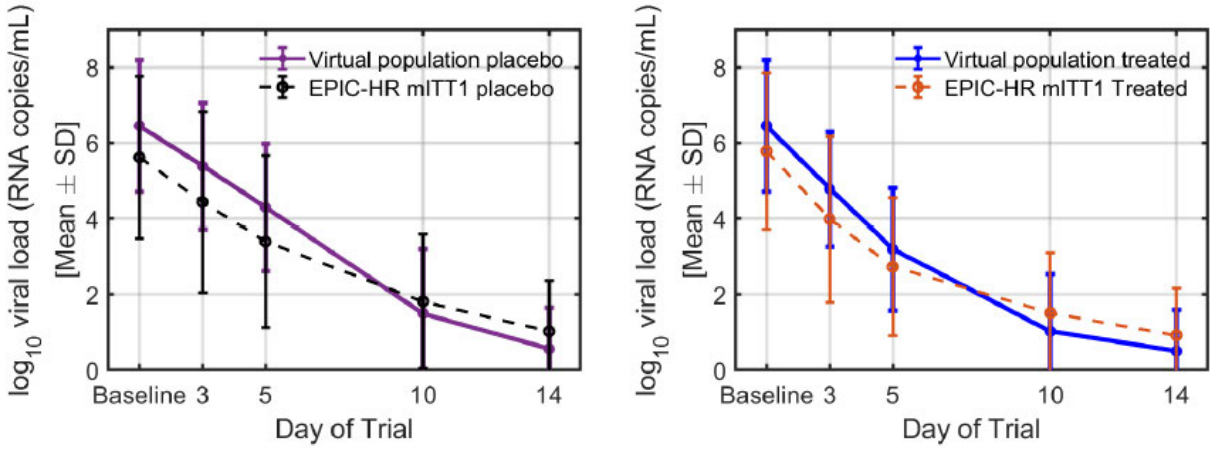
The immunocompromised patients are expected to exhibit a significantly longer viral RNA shedding than immunocompetent high-risk outpatient population. The immunocompromised virtual population was formulated using two approaches (bottom-up and top-down) to reproduce the expected viral dynamics mechanistically or phenotypically:

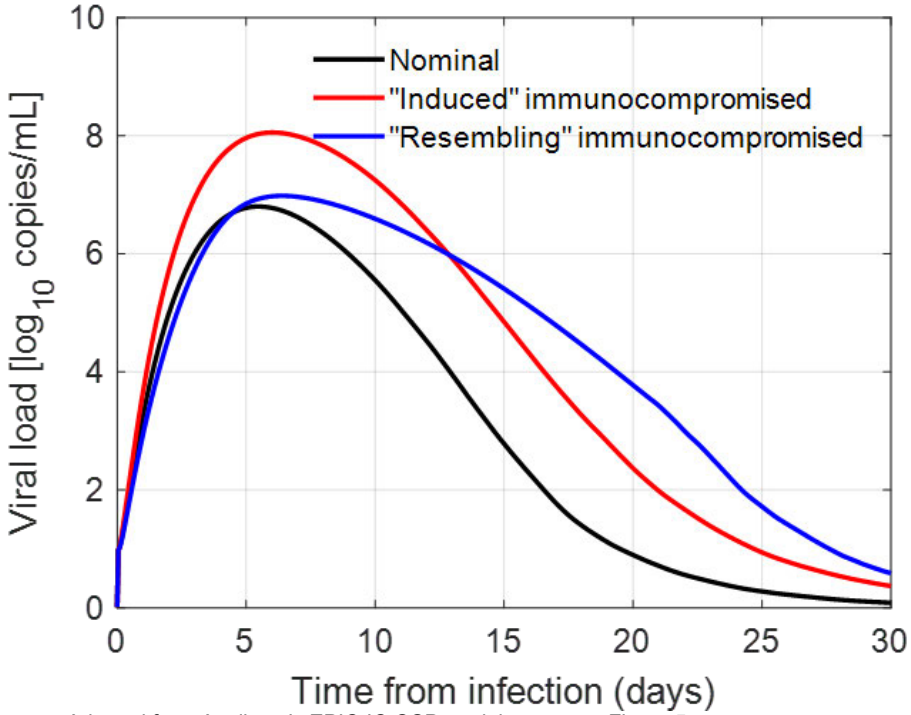
- Bottom-up approach: The bottom-up approach refers to an induced immunosuppression based on the mechanistical understanding of key components (i.e., Type I IFN, $CD8^+$ T cells) critical in mounting an effective immune response. For each subject in the nominal population, the values of the three parameters relating to the anti-viral effects was decreased by a factor of 2 (km_int_IFNb: IC_{50} of Type I IFN, k_IFNb_kill: rate constant for induction of infected cell clearance by Type I IFN, k_kill: rate constant for infected cell clearance by $CD8^+$ cell). The virtual population was then trimmed to exclude those with viral RNA shedding >10^3 copies/mL by day 75 of the initial viral inoculum. The resulting virtual patients (n = 505), also referred to as "induced" immunocompromised patients, exhibit a higher peak viral RNA shedding and a prolonged viral shedding upon infection (Figure 43).
- Top-down approach: The top-down approach refers to the selection or enrichment of a subset from virtual population that presents a prolonged viral shedding. The selection criterium is the subjects with duration of viral RNA shedding (from viral RNA shedding peak to <10^2 copies/mL) in the top 85th percentile of the nominal virtual population. The selected virtual patients, also referred to as "resembling" immunocompromised patients, naturally exhibit a longer viral shedding than the overall virtual patients (Figure 43).

Figure 42. Aggregate Viral Load Time Course for Placebo (Left) and Treatment (Right) of the Virtual Population and EPIC-HR mITT1 Study Population.



Source: Applicant's IR response submitted on February 1, 2023, Figure 1.
Note: The spanning bar represents SD of viral load at each nominal time point.
Abbreviations: log, logarithm; mITT, modified intent to treat; RNA, ribonucleic acid; SD, standard deviation

Figure 43. Example Mean Viral Dynamic in Immunocompromised Virtual Patients Using Two Independent Approaches



Source: Adapted from Applicant's EPIC-IC QSP model summary, Figure 5.
Note: The top-down approach to preferentially select a cohort of virtual subjects [blue line, N=110] with prolonged viral shedding that resembles viral dynamics in immunocompromised patients, and a bottom-up approach [red line, N = 505] that mechanistically induces immunosuppression by diminishing the effect of the immune response in a nominal virtual population [Solid Black Line]
Abbreviations: log, logarithm; N, total number of subjects; QSP, quantitative systems pharmacology

Evaluation of Treatment Duration in Immunocompromised Patients

To identify the appropriate treatment duration in immunocompromised patients, QSP model was applied to predict viral dynamics in the two immunocompromised virtual populations. Viral RNA shedding reduction across different durations of treatment was graphically explored by the Reviewer and showed a maximal viral suppression on average around Day 10 in both immunocompromised virtual populations (Figure 44). Applicant summarized viral RNA shedding rebound with the lower and upper bound informed by the more extreme values of pooled event rates from the two immunocompromised virtual populations. The odds ratio relative to the nominal virtual population (high-risk immunocompetent population) treated with 5-day PAXLOVID was calculated using the equation below:

Equation 1. Odds Ratio Relative to the Nominal Virtual Population Following 5 Days of Paxlovid Treatment

$$Odds\ ratio = \frac{\%\ VLR\ of\ X\ days\ treatment\ in\ immunocompromised}{\%\ VLR\ of\ 5\ days\ treatment\ in\ immunocompetent}$$

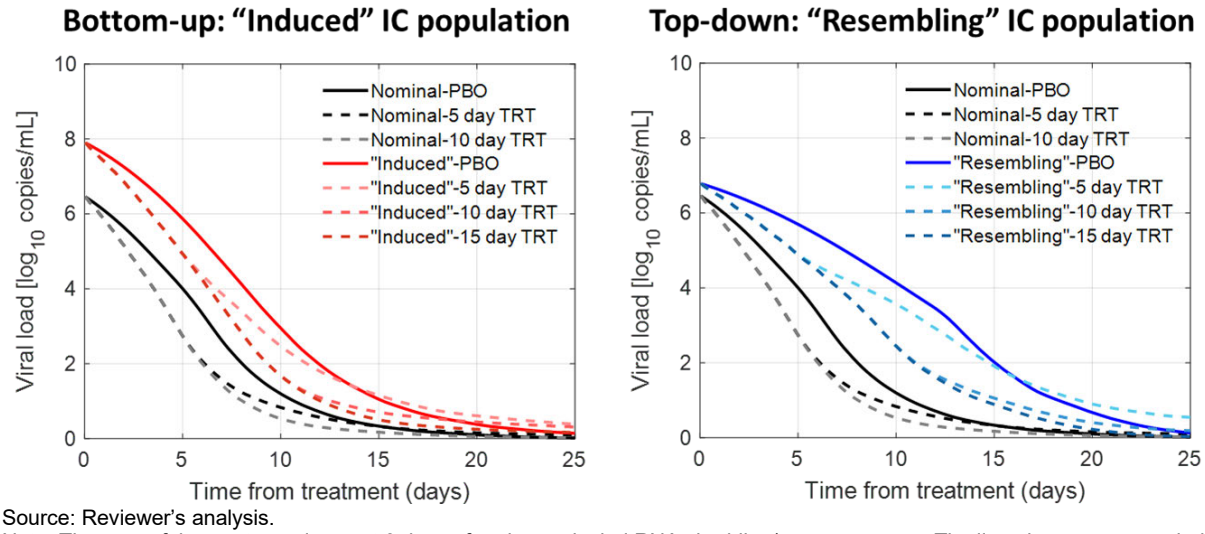
Source: FDA reviewer.
Abbreviations: VLR, viral load rebound

The viral RNA shedding rebound in the Applicant's analysis is defined as positive slope post treatment termination (see example of viral RNA shedding rebound in individual virtual subjects

in Figure 45). As shown in Figure 46, the risk of rebound upon treatment termination is substantially reduced with 10 days of treatment and is predicted to be more comparable to that in a high-risk immunocompetent population. Extending the treatment to 15 days is not predicted to lead to further benefit in mitigating the risk of viral RNA shedding rebound.

It is worth noting that the nominal virtual population was only calibrated to the observed rate of post-treatment viral RNA shedding rebound in the treatment arm with no regards to the observed rate of viral RNA rebound in the placebo arm. Therefore, the comparison for viral RNA rebound is only interpreted under the treatment condition. Another caveat is the inconsistent time frame to capture viral RNA rebound between the numerator and denominator of odds ratio. As noted in the viral RNA rebound definition, the event is captured post treatment termination, therefore, for treatment longer than 5 days in the numerator, the effect on viral RNA rebound is a combined effect of time elapse and treatment, despite that few viral RNA rebound events are expected during treatment. In order to minimize the time dependent effect on viral RNA rebound, a consistent time frame instead of post treatment (i.e., 5 days after the treatment) was used to recalculate odds ratio for different duration of treatment in immunocompromised virtual patients in a sensitivity analysis by Reviewer. The result agrees with Applicant's result that the risk of viral RNA rebound with 10 days of treatment in immunocompromised virtual populations is comparable to that with 5 days of treatment in a high-risk immunocompetent population (Figure 46).

Figure 44. Predicted Mean Viral Dynamic With Longer Treatment Duration in the Two Immunocompromised Virtual Patients



Source: Reviewer's analysis.
Note: The start of the treatment is set at 3 days after the peak viral RNA shedding/symptom onset. The line shows average viral RNA shedding over time.
Abbreviations: IC, immunocompromised; log, logarithm; PBO, placebo; RNA, r bonucleic acid; TRT, treatment

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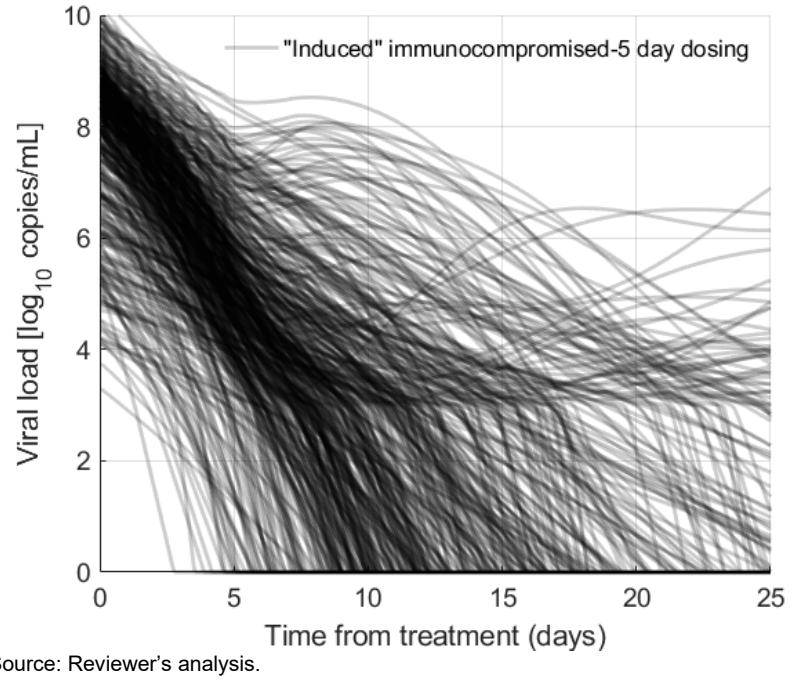
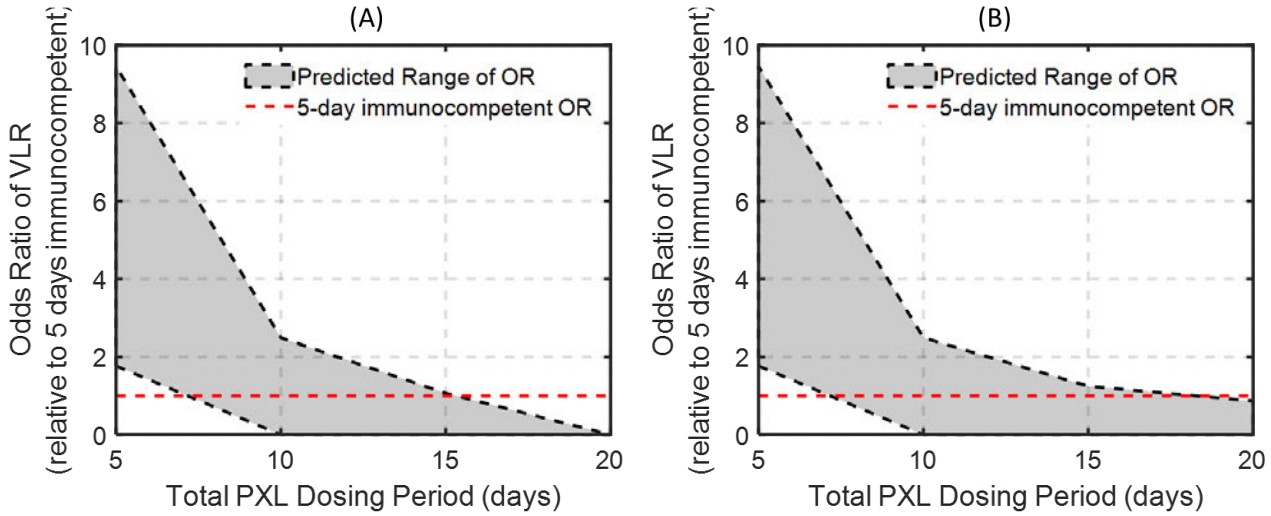
Figure 45. Viral Dynamics in Immunocompromised Virtual Patients With 5 Days of Dosing



Source: Reviewer's analysis.
Abbreviations: log, logarithm

Figure 46. Predicted Risk of Viral Load Rebound in Immunocompromised Patients for Increasing PAXLOVID Dosing Duration Relative to the Risk of Rebound Upon 5 Days of Dosing in a High-Risk Immunocompetent Population



Source: Adapted from Applicant's EPIC-IC QSP model summary, Figure 6.
Note: (A) Applicant's analysis, (B) Reviewer's analysis that differs in the time frame for capturing viral RNA rebound event.
Abbreviations: OR, odds ratio; PXL, paxlovid; QSP, quantitative systems pharmacology; RNA, ribonucleic acid; VLR, viral load rebound

The submitted QSP models were calibrated and validation with various sources of observational and interventional clinical data. The prospective simulations with the submitted QSP models were used to inform the treatment duration of PAXLOVID in EPIC-HR. Efficacy of PAXLOVID was later demonstrated in this trial, and the data were used to refine the QSP model

such that it better captures the aggregate viral RNA shedding time course profiles in target population with or without treatment. Thus, the proposed QSP modeling as well as parameters sampled in virtual population are appropriate for depicting an average viral dynamics profile in mild-to-moderate COVID-19 outpatient population. To select the treatment duration for immunocompromised patients, the same modeling approach was adapted by developing a virtual population for immunocompromised patients. Results of QSP simulations showed that the treatment duration of 5 days, as indicated in the current EUA fact sheet and proposed label, might not be optimal for immunocompromised patients. Reviewer concluded that QSP modeling approach is appropriate in support of selecting treatment duration for the clinical trials in the overall PAXLOVID-eligible population (EPIC-HR trial) as well as immunocompromised patients (ongoing EPIC-IC trial).

14.5.2.7. Assessment of Model Risk

Table 106. Assessment of Model Risk

Assessment	Description[1]	Comments
Context of use	Describe the specific issue(s) that the QSP analyses will be used to address	Using QSP modeling approach to evaluate the optimal treatment duration for immunocompromised patients being tested in clinical trial, EPIC-IC.
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Medium: QSP analyses provide predictions of viral dynamics under various exposure scenarios. Simulations results were used to support the selection of treatment duration in EPIC-IC. Clinical data from EPIC-HR are also used to inform the trial design of EPIC-IC.
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low: The efficacy and safety have been established by EPIC-HR, EPIC-SR, and EPIC-PEP, and PAXLOVID is used widely in real-world. Risks of therapeutic failure or unknown adverse effects in immunocompromised patients receiving PAXLOVID, based on current and upcoming information from EPIC-IC, are considered low.

Source: Reviewer's analysis.
1. (Kuemmel et al. 2020).
Abbreviations: QSP, quantitative system pharmacology

14.5.3. Applicant's Population PK Analysis

14.5.3.1. Objectives

The primary objectives of the Applicant's analysis were to:

- Characterize the PK of nirmatrelvir in healthy adults and mild-to-moderate COVID-19 patients.
- Evaluate time- and dose-dependent change in PK.

14.5.3.2. Overview of Studies Included in Population PK Analysis

Applicant conducted a population PK analysis to characterize the PK of nirmatrelvir in the presence of ritonavir (RTV) which is used to inhibit CYP3A-mediated metabolism of nirmatrelvir, identified covariate factors that could affect disposition, and exported the individual exposure estimates for subsequent exposure-response (E-R) analysis. Population PK analysis included the studies listed in Table 107.

Table 107. Clinical Studies Used in Population PK Analysis

Study (n)	Description	Dose and Sampling Time
C4671001 (n=43)	A Phase 1 randomized, single- and multiple-dose escalation study to evaluate the safety, tolerability, and PK of NIR in healthy adult participants	Single Dose • 250 mg, 300 mg, 750 mg Multiple Doses • Repeated: 75 mg/250 mg/500 mg q12h • Intense: 750 mg at 0,2, & 4 hours PK Sampling • Rich sampling up to 72 hours for single dose, up to 12 hours on Days 1, 5, & 10 for multiple repeated doses, up to 96 hours for multiple intense doses.
C4671010 (n=16)	A Phase 1 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Dose • Single 100 mg dose PK Sampling • Rich sampling up to 48 hours
C4671010 (n=34)	A Phase 1 study to assess the PK, safety, and tolerability of NIR/RTV in adult participants with renal impairment and in healthy participants with normal renal function	Dose • Single 100 mg dose PK Sampling • Rich sampling up to 48 hours
C4671012 (n=23)	A Phase 1 crossover study to estimate the effect of NIR/RTV and RTV on the PK of dabigatran (a P-gp substrate) in healthy participants	Dose: • 300 mg q12h for 3 doses PK Sampling: • Rich sampling up to 48 hours on Day 2
C4671013 (n=11)	A Phase 1 crossover study to estimate the effect of NIR/RTV and RTV on the PK of midazolam (a CYP3A substrate) in healthy participants	Dose • 300 mg q12h for 9 doses PK Sampling • Rich sampling up to 72 hours on Day 5
C4671014 (n=12)	A Phase 1 crossover study to estimate the effect of carbamazepine (a strong CYP3A inducer) on the PK of NIR/RTV in healthy participants	Dose • Single dose: 300 mg PK Sampling • Rich sampling up to 48 hours

Study (n)	Description	Dose and Sampling Time
C4671015 (n=11)	A Phase 1 crossover study to estimate the effect of itraconazole (a strong CYP3A inhibitor) on the PK of NIR/RTV in healthy participants	Multiple Dose • 300 mg q12h for 5 doses PK Sampling • Rich sampling up to 72 hours on the last day of dosing
C4671005 EPIC-HR (n=1087)	A Phase 2/3 study to investigate orally administered NIR/RTV compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	Multiple Dose • 300 mg q12h for 10 doses PK Sampling • 1 sample collected 30-90 min post-dose on Day 1, 1 predose sample on Day 5.

Source: Applicant's PK report, Table 1.
Note: Synopsis of clinical data that only included the cohorts/treatment arms with 100 mg ritonavir co-administration.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CYP3A, cytochrome P450, family 3, subfamily A; n, number of subjects in sample; NIR, nirmatrelvir; P-gp, P-glycoprotein; PK, pharmacokinetic; q12h, every 12 hours; RTV, ritonavir

14.5.3.3. Population PK Model

The population PK analysis was conducted via nonlinear mixed-effects modeling with the *NONMEM* software, version 7.5.0 using first-order conditional estimation with *INTERACTION* option (*FOCEI*).

Baseline patient characteristics of the population PK dataset are summarized in Table 108. A total of 2408 samples from healthy participants and 1996 ambulatory COVID-19 patients (EPIC-HR) were included for the population PK analysis. BLQ accounts for 14% of PK samples in the pooled data and 20% of PK samples in EPIC-HR study. Majority of BLQ samples are post-dose and within 24 hours of dosing. Post-dose BLQ after single dose of NIR/RTV co-administration was not observed in Phase 1 studies when the drug was taken at full compliance. In EPIC-HR, the large proportion of BLQ samples could be due to the nature of this study design that non-compliance or inaccurate documentation of dosing and/or sampling time is plausible. Concentrations collected before the first dose were excluded from the PK analysis as well as post-dose observations that were below the limit of quantification (BLQ).

Covariates explored included age, body weight, sex, race, GMI, creatinine clearance, disease status (heathy, coronavirus disease [COVID], hepatic impaired), CYP3A inhibitors/inducers, dose, and formulation.

The final population PK parameters for nirmatrelvir with RTV co-administration are presented in the Table 109. The final PK models were parameterized in terms of Ka, CL, V2, Q, and V3. Covariates including COVID-19 disease, CYP3A inducer/inhibitor, formulation, dose, age were statistically significant.

Estimated fixed and random effect parameters were estimated with good precision (percent relative standard error [%RSE] <30%) with the exception of IIV of CL (35.9% RSE). The magnitude of the IIV was moderate to high except IIV of V2 which was 27.3%. Residual variability was small for phase 1 data, but high for phase 2/3 data which are exclusively from EPIC-HR. ETA shrinkages are moderate to high (>50%) for all parameters.

The diagnostic plots showed no obvious bias in prediction relative to observations across the time range, however, there appears to be some bias across concentrations (Figure 47). The bias is primarily observed for concentrations from EPIC-HR (C4671005) which might be due to the inaccuracy of dosing/sampling and other reasons related to compliance of the trial (Figure 48). Visual predictive check for the final PK models were stratified by dose (Figure 49). There was bias between prediction and observations observed in EPIC-HR for high and low concentrations but not for median concentrations. Overall, the prediction corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations.

Table 108. Patient Characteristics in NIR PK Analysis Dataset

Characteristics	All (n=1237)	COVID-19 (n=1087)	Healthy (n=150)
Race			
White	865 (69%)	777 (62%)	88 (7%)
Black	105 (8%)	56 (4%)	49 (4%)
Asian	162 (13%)	152 (12%)	10 (1%)
American Indian	95 (8%)	95 (8%)	0
Other/unknown	10 (1%)	7 (1%)	3 (0%)
Intrinsic Factors			
Female, n (%)	580 (46%)	541 (43%)	39 (3%)
Body weight (kg), median (range)	79 (42-158)	80 (42-158)	77 (53-114)
Age (years), median (range)	45 (18-86)	45 (18-86)	49 (20-76)
Baseline Values			
Baseline BSA, normalized CLCR (mL/min/1.73m^2), median (range)	119 (16-318)	124 (23-318)	96 (16-247)
Baseline BMI (kg/m^2), median (range)	28 (17-58)	28 (17-58)	27 (20-40)

Source: Applicant's PK report, Table 6.
Abbreviations: BMI, body mass index; BSA, bovine serum albumin; CLCR, creatinine clearance; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; n, number of subjects in sample; NIR, nirmatrelvir; PK, pharmacokinetic

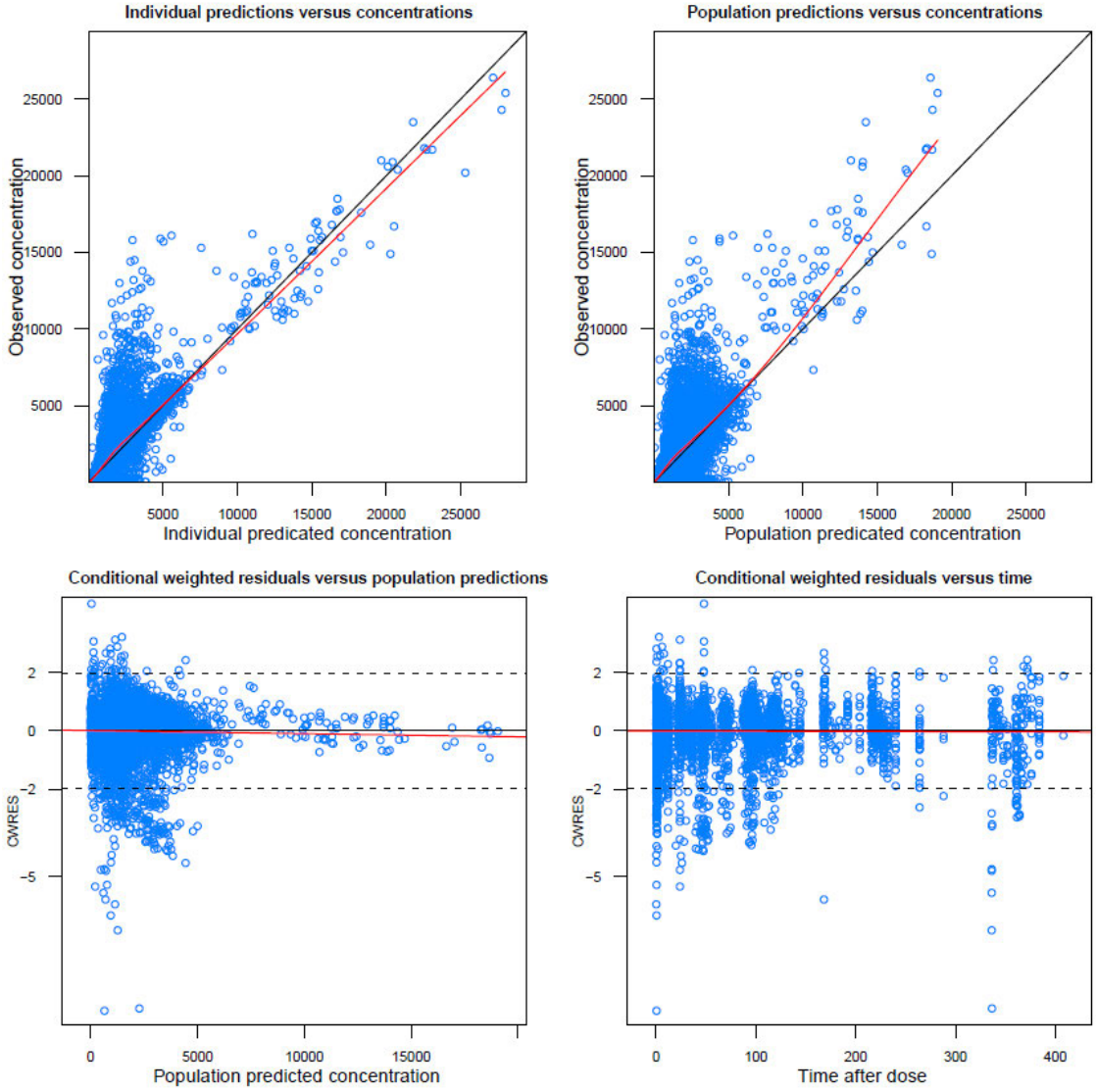
Table 109. Population Pharmacokinetic Model Parameters for NIR With RIT Co-Administration

	Final Run			Sampling Importance Resampling Run
Parameter	Estimate	% RSE	Shrinkage (%)	Median (2.5th, 97.5th percentile)
CL (L/h)	9.09	3.6		8.98 (8.53, 9.42)
V2 (L)	56.9	4.3		57.5 (53.6, 62.6)
Q (L/h)	1.28	14.2		1.02 (0.704, 1.36)
V3 (L)	12.8	11.1		10.1 (8.22, 12.7)
Ka (1/h)	0.873	8.9		0.908 (0.791, 1.03)
$nCLCR_{breakpoint}$ (mL/min/1.73m^2)	70.1	0.03		70.1 (70.0, 70.1)
$nCLCR_{power}$ for <$nCLCR_{breakpoint}$	1.05	8.4		0.907 (0.748, 1.09)
$F1_{power}$	-0.409	8.7		-0.401 (-0.458, -0.341)
Effect of COVID-19 on CL	-0.341	10.7		-0.348 (-0.410, -0.288)
Effect of Carbamazepine on CL	0.74	27.1		0.740 (0.583, 0.939)
Effect of Itraconazole on CL	-0.308	7.2		-0.303 (-0.332, -0.272)
Power of age effect on V2	-0.425	17.6		-0.416 (-0.553, -0.285)
Effect of 150 mg tablet on F1	-0.379	10.1		-0.391 (-0.454, 0.331)
IIV-CL (%CV)	35.9	48.8	55.9	35.7 (30.5, 42.9)
IIV-V2 (%CV)	27.3	17.6	68.8	31.2 (27.5, 34.1)
IIV-V3 (%CV)	58.7	26.6	79.2	59.2 (44.9, 71.6)
IIV-Ka (%CV)	60.7	20.9	63.1	60.5 (51.7, 68.6)

Parameter	Final Run Estimate	% RSE	Shrinkage (%)	Sampling Importance Resampling Run Median (2.5th, 97.5th percentile)
Proportional error Phase 1 (%)	32.4	5.7	6.28	31.9 (30.7, 33.4)
Proportional error Phase 2/3 (%)	139	3.8		136 (131, 142)
Additive error (ng/mL)	10 fixed			

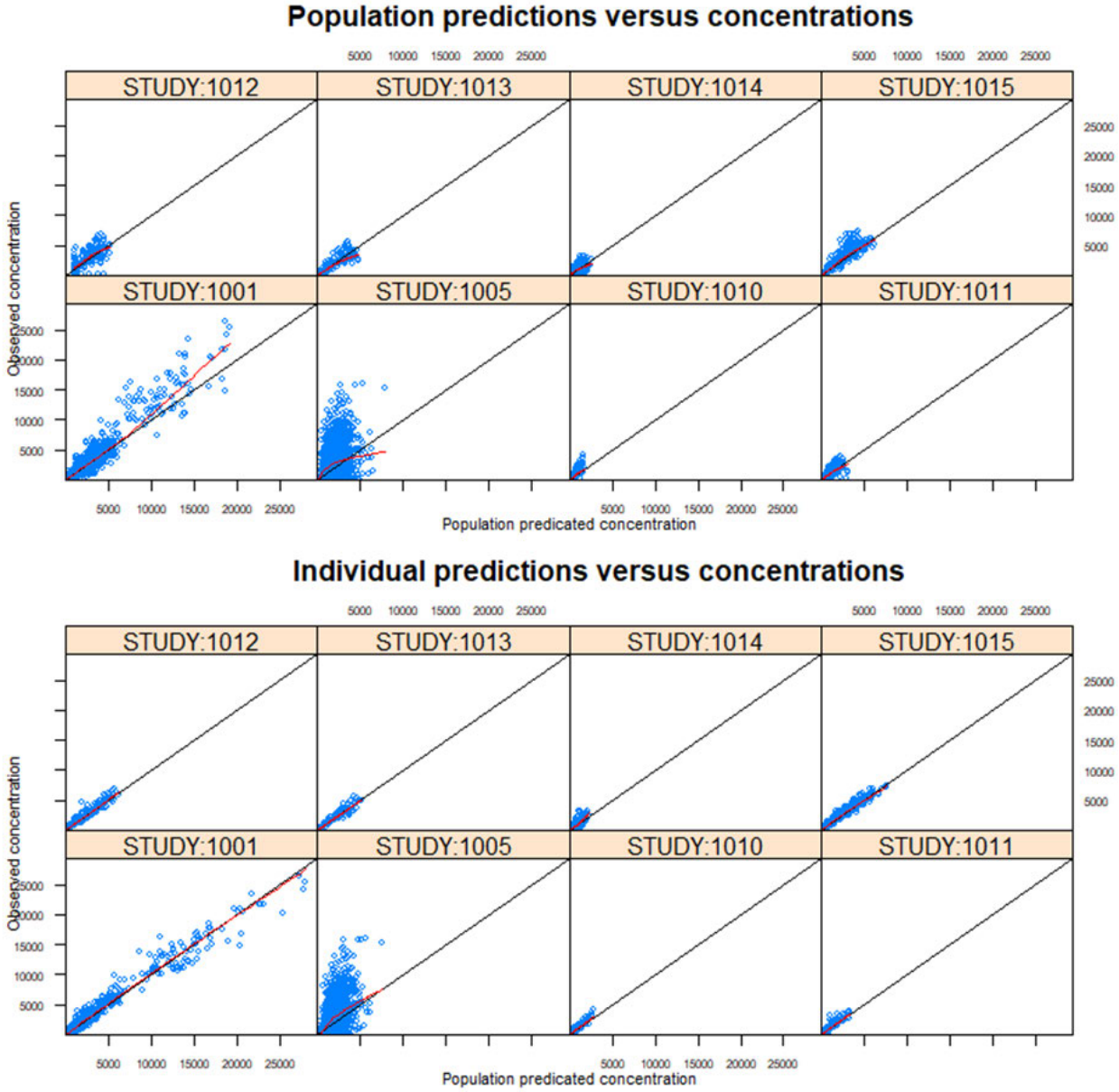
Source: Applicant's PK report, Table 12.
Note: Weight effect is parameterized as (Weight/70 kg)^0.75 on CL and Q, and (Weight/70 kg)^1 on V2 and V3
Note: Effect of COVID-19, Carbamazepine, or itraconazole was parameterized as a proportional shift of (1+THETA) on CL.
Note: Power of age effect = exponent for (Age/45 years) on V2.
Abbreviations: CL, apparent clearance of NIR; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; CV, coefficient of variation; F1, relative bioavailability; $F1_{power}$, exponent of power function for (Dose/300 mg) on F1; IIV, interindividual variability; Ka, first-order absorption rate constant; nCLCR: body surface area-normalized creatinine clearance; $nCLCR_{breakpoint}$, breakpoint for nCLCR effect on CL; $nCLCR_{power}$, exponent of power function for (nCLCR/70.1 mL/min/1.73m^2) on CL; NIR, nirmatrelvir; PK, pharmacokinetic; Q, inter-compartmental clearance; RIT, ritonavir; %RSE, percent relative standard error; V2, central volume of distr bution; V3, peripheral volume of distr bution

Figure 47. Goodness-of-Fit for NIR Population PK Model



Source: Reviewer's analysis.
Abbreviations: CWRES, conditional weighted residuals; NIR, nirmatrelvir; PK, pharmacokinetic

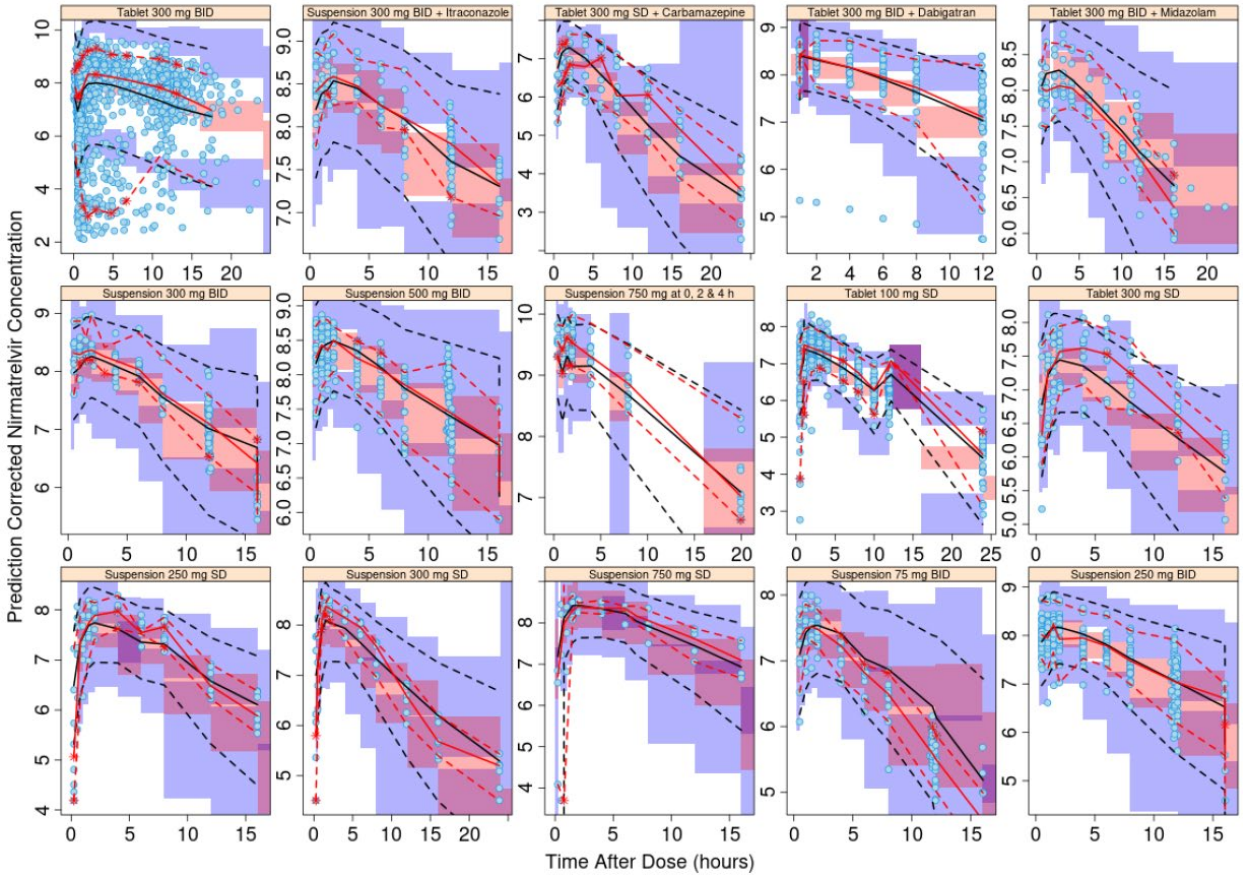
Figure 48. Prediction vs. Concentrations by Study



Source: Reviewer's analysis.

Reference ID: 5179402

Figure 49. Visual Predictive Check for NIR Population PK Model Stratified by Treatment



Source: Applicant's PK report, Figure 4.
Note: Symbols = observed NIR concentrations; Red solid and broken lines = median, 5th & 95th confidence intervals of the observed data; Black solid and broken lines = median, 5th & 95th confidence intervals from 1000 simulations with surrounding 95% shaded area in pink and blue. Excluded observations with time after dose ≥24 hours.
Abbreviations: BID, twice daily; NIR nirmatrelvir; PK, pharmacokinetic; SD, single dose

The PK model appropriately described the data for both PK/pharmacodynamic (PD) modeling and descriptive labeling purposes. A large proportion of post-dose BLQ is observed which is unlikely to be related to the property of drug disposition. The evaluable concentrations were quantifiable for reliable estimation of PK parameters in the two-compartment model with first-order absorption. The Applicant indicated that there is bias between the observed and predicted concentrations in EPIC-HR (C4671005) only. It is because that PK sampling/dosing schedule in this trial was inaccurate. We notice that the dosing schedule is obtained through subject log only in this trial, not for others. It might provide a possible explanation on the bias. ETA shrinkage is high and would not generate credible individual parameter estimates in E-R analysis.

14.5.4. Applicant's Exposure-Response Analyses

14.5.4.1. Overview of Studies Included in the E-R Analysis

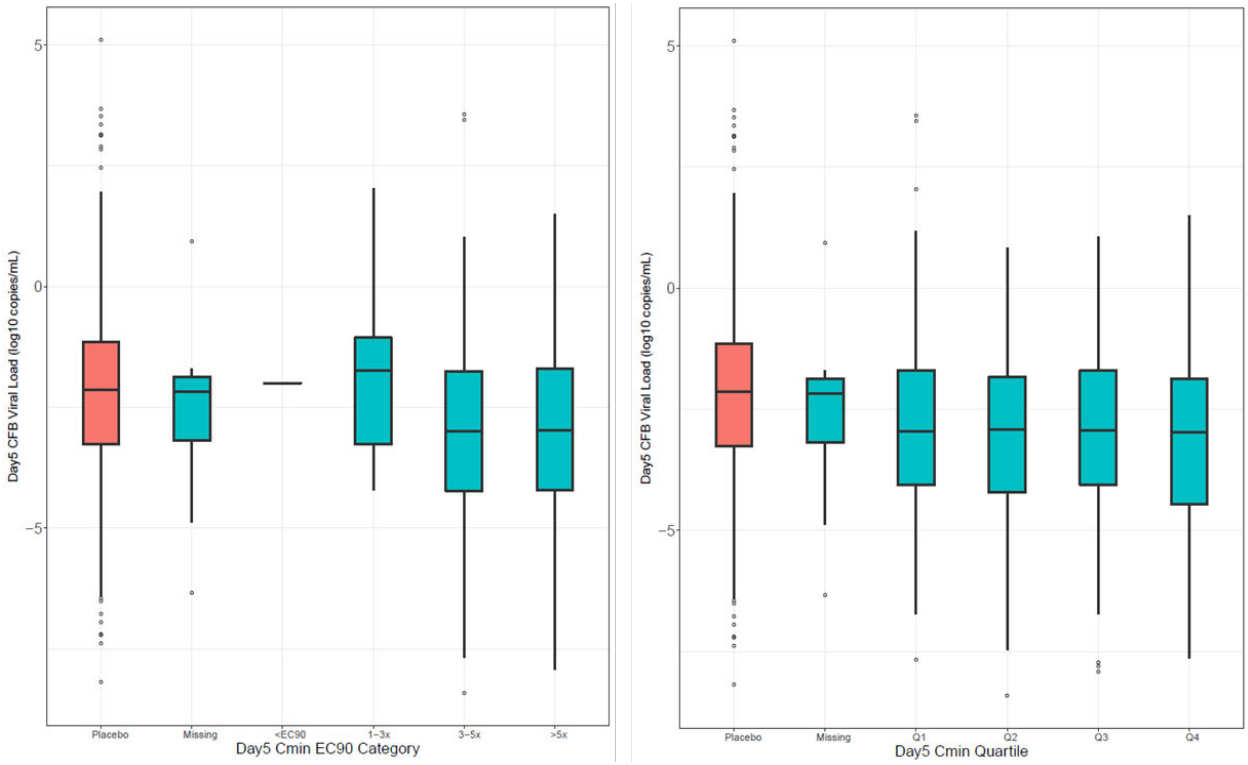
Efficacy and safety data from the EPIC-HR was utilized for the E-R analyses. Exploratory analyses were conducted using R version 3.6.1 or later.

Reference ID: 5179402

14.5.4.2. E-R for Efficacy

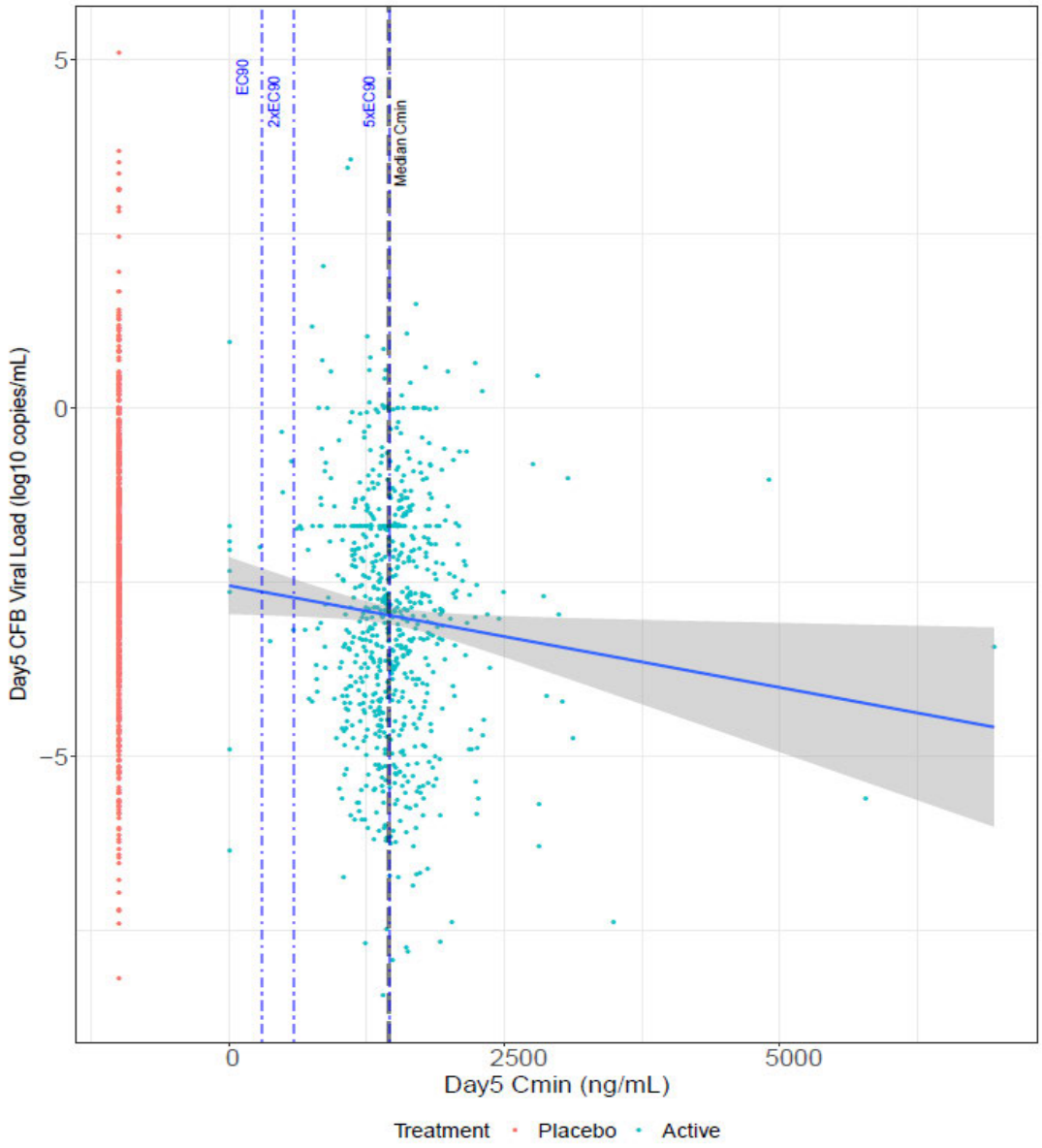
E-R relationship between the change from baseline in viral RNA shedding and C_{min} at Day 5 of treatment was explored by categorizing C_{min} relative to nirmatrelvir in vivo EC_{90} value (i.e., <EC_{90}, 1-3x EC_{90}, 3-5x EC_{90}, and >5x EC_{90} values) or in quartiles (Figure 50). Linear regression was also conducted which predicted a small slope for C_{min}, which predicts to a 0.08 reduction in viral RNA shedding (in Log_{10} copies/mL) for an increase of 1 EC_{90} (Figure 51). This seemingly suggests an enhanced viral clearance with an increased concentration; however, the variability is very large across concentrations and few concentrations in PAXLOVID treated patients were under 3x EC_{90} value. By comparison across quartiles, there was no obvious difference in the change from baseline in viral RNA shedding.

Figure 50. Day 5 Change From Baseline in Viral Load by D5 NIR C_{min} Relative to EC_{90} Value or in Quartiles



Source: Applicant's ER-efficacy report, Figure 1 and 2.
Note: Placebo participants represented in red, active PAXLOVID treatment participants represented in blue. Boxes extend from 25th to 75th percentiles with center line representing median; whiskers extend to 1.5 times the inter-quartile range with individual dots representing outlying points.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; D5, Day 5; EC90, 90% maximal effective concentration; ER, exposure-response; log, logarithm; NIR, nirmatrelvir; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4

Figure 51. Day 5 Change From Baseline in Viral Load by D5 NIR C_{min}



Source: Applicant's ER-efficacy report, Figure 3.
Note: Linear regression line shown in solid blue with associated 95% confidence interval in gray. Median predicted Day 5 C_{min} shown with black dashed line; EC90 value reference lines shown with blue dot-dash lines. Placebo participants represented in red, active PAXLOVID treatment participants represented in blue.
Abbreviations: CFB, change from baseline; C_{min}, minimum plasma concentration; D5, Day 5; EC90, 90% maximal effective concentration; ER, exposure-response; log, logarithm; NIR, nirmatrelvir

14.5.4.3. E-R for Safety

E-R relationship between major safety events and observed/suspected lab abnormalities and exposures at Day 5 of treatment (i.e., C_{max}, C_{min}, AUC_{tau}) was explored by categorizing the exposure in quartiles.

The analysis included the following AE/lab abnormalities:

- Safety events
  - Grade ≥1 dysgeusia
  - Grade ≥1 diarrhea, headache
  - Grade ≥1 vomiting
  - Grade ≥1 nausea
  - Grade ≥1 hypertension
- Lab abnormalities
  - Activated partial thromboplastin time (aPTT) >1.1x upper limit of normal (ULN)
  - Prothrombin time (PT) >1.1x ULN
  - Platelets <0.5x lower limit of normal (LLN)
  - Platelets >1.75x ULN
  - Leukocytes <0.6x LLN
  - Leukocytes >1.5x ULN
  - Glucose >1.5x ULN
  - Creatinine kinase >2.0x ULN
  - Fibrinogen >1.25x Baseline
  - D-Dimer >1.5x ULN

Univariate logistic regression was conducted for the selected safety endpoints. Table 110 summarizes the event number, exposure in the final model (selected by the largest deviance and smallest p-value among the exposure metrics), p-value for logistic regression, and AUC of receiver-operating characteristic curve. The significant E-R relationships were identified for Grade ≥1 dysgeusia, Grade ≥1 diarrhea, leukocytes <0.6x LLN, and fibrinogen >1.25x baseline. Among them, all expect dysgeusia had either few events or AUC_{ROC} close to 0.5 which indicates poor model predictive performance. For dysgeusia, a positive relationship was observed but the slope was relatively flat for 95% of predicted C_{max} (Figure 52). The predicted probability of Grade ≥1 dysgeusia at the maximal predicted C_{max} with an event is 13%.

Table 110. E-R Analysis for Safety Events in EPIC-HR

AEs	Grade Assessed	Event Number (%)[a]	Exposure in Final Model	Slope	p-value for E-R	AUC_{ROC}
Dysgeusia	≥ Grade 1	63 (2.86%)	C_{max} (ng/mL)	0.000502	p<0.0001	0.742 (0.697-0.788)
Headache	≥ Grade 1	30 (1.36%)	C_{min} (ng/mL)	3.47E-05	p=0.8765	0.514 (0.411-0.616)
Diarrhea	≥ Grade 1	52 (2.36%)	C_{min} (ng/mL)	0.000369	p=0.0158	0.593 (0.518-0.668)
Nausea	≥ Grade 1	34 (1.54%)	C_{max} (ng/mL)	1.93E-05	p=0.8424	0.512 (0.408-0.617)
Vomiting	≥ Grade 1	21 (0.95%)	C_{max} (ng/mL)	0.000119	p=0.3216	0.564 (0.434-0.694)
Hypertension	≥ Grade 1	8 (0.36%)	C_{max} (ng/mL)	0.000324	p=0.0899	0.693 (0.494-0.892)

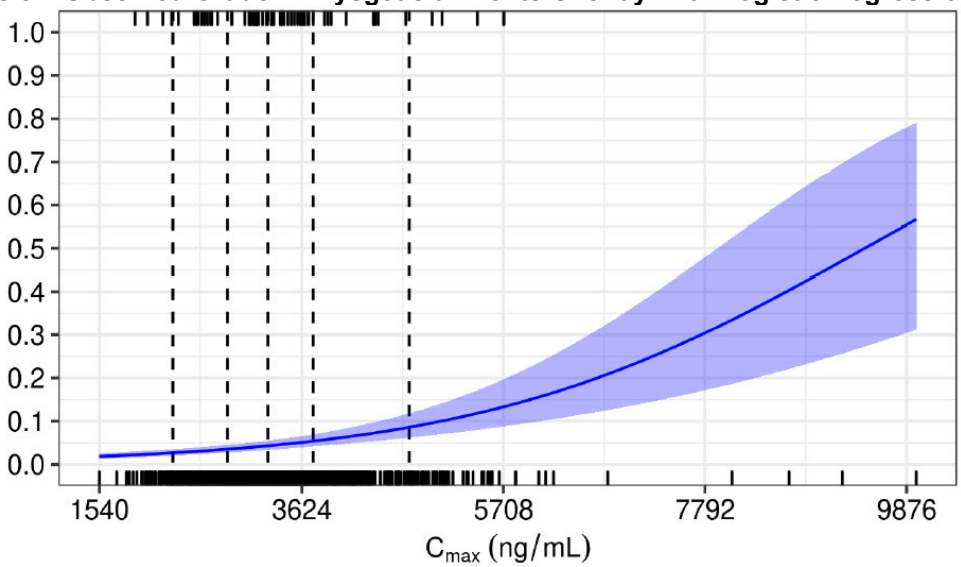
Source: Applicant's clinical pharmacology IR response on August 30, 2022, Table 1 and 2; Synopsis from Applicant's ER-safety report.
[a.] Event numbers includes all participants regardless of treatment group. % = % total of study participants.
Abbreviations: AE, adverse event; AUC_{ROC}, area under the receiving operating characteristic curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E, exponentiation with base 10; E-R, exposure-response

Table 111. E-R Analysis for Lab Abnormalities in EPIC-HR

Lab Test (Unit)	Clinical Cut-Off	Event Number (%)[a]	Exposure in the Final Model	Slope	p-value for E-R	AUC_{ROC}
aPTT (sec)	> 1.1 x ULN	366 (16.62%)	C_{max} (ng/mL)	-1.61E-05	p=0.6203	0.507 (0.477-0.537)
Prothrombin time (sec)	> 1.1 x ULN	202 (9.17%)	C_{min} (ng/mL)	-7.91E-05	p=0.3922	0.515 (0.473-0.554)
Platelets (10^9/L)	<0.5 x LLN	5 (0.23%)	AUC_{tau} (ng*hr/mL)	0.000876	p=0.9928	0.747 (0.737-0.758)
Platelets (10^9/L)	> 1.75 ULN	15 (0.68%)	C_{min} (ng/mL)	0.000361	p=0.3079	0.56 (0.417-0.703)
Leukocytes (10^9/L)	< 0.6 x LLN	10 (0.45%)	AUC_{tau} (ng*hr/mL)	-6.70E-05	p=0.0493	0.68 (0.548-0.813)
Leukocytes (10^9/L)	>1.5 x ULN	25 (1.14%)	C_{max} (ng/mL)	7.59E-05	p=0.4949	0.528 (0.428-0.627))
Glucose (mg/dL)	>1.5 x ULN	156 (7.08%)	C_{min} (ng/mL)	-4.58E-05	p=0.6576	0.482 (0.442-0.523)
Creatinine Kinase (U/L)	> 2.0 x ULN	116 (5.27%)	C_{min} (ng/mL)	0.00012	p=0.2912	0.516 (0.467-0.564)
Fibronogen (mg/dL)[b]	> 1.25 x baseline	413 (18.76%)	AUC_{tau} (ng*hr/mL)	-1.50E-05	p<0.0001	0.558 (0.53-0.587)
D-Dimer[b]	> 1.5 x ULN	325 (14.76%)	C_{min} (ng/mL)	0.000169	p=0.0274	0.551 (0.519-0.583)

Source: Applicant's clinical pharmacology IR response on August 30, 2022, Table 1 and 2; Synopsis from Applicant's ER-safety report.
[a.] Event numbers includes all participants regardless of treatment group. %=% total of study participants.
[b.] Treatment-emergent AEs.
Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; AUC_{ROC}, area under the receiving operating characteristic curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E, exponentiation with base 10; E-R, exposure-response

Figure 52. Observed Grade ≥1 Dysgeusia Events Overlay With Logistic Regression Model



Source: Applicant's ER-safety report, Figure A2.2.
Note: The vertical dashed lines represent the observed 0.05, 0.25, 0.5, 0.75 and 0.95 quantiles of the dependent variable.
Abbreviations: C_{max}, maximum plasma concentration; E-R, exposure-response

In the Applicant's analyses for efficacy and safety based on the data from EPIC-HR, a flat relationship was generally observed across the exposure range (or substantial part if not all) for viral RNA shedding reduction from baseline and safety endpoints. The analysis is considered exploratory with caveats of narrow exposure range and inaccurate individual exposures due to moderate to high ETA shrinkages in population PK analysis. The results/conclusions thus require further evaluation with the clinical data.

14.6. Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- Evaluate the drug-drug interaction (DDI) potential of nirmatrelvir, in the nirmatrelvir/ritonavir combination product, as a victim of moderate and weak CYP3A inducers.

The Division of Pharmacometrics has reviewed the PBPK reports (032551, 083028 and 074428), the responses to Food and Drug Administration's (FDA's) information requests (resp-fda-clin-

pharm-ir-05oct2022, resp-fda-ir-pbpk-01-nov-2022, response-30-oct-22-ir-alt-dosage, resp-13dec2022-ir-clin-pharmacology), and the modeling supporting files to conclude that:

- The ritonavir model used by the Applicant is inadequate to predict the effects of CYP3A inducers on the exposure of nirmatrelvir/ritonavir combination.
- The reviewer used an alternative ritonavir model and predicted that weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ritonavir 300/100 mg product.

Background

Nirmatrelvir (also known as PF-07321332) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, currently being developed for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death. PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) co-packaged with 100 mg ritonavir (one 100 mg tablet). Ritonavir is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. These three tablets must be taken together twice daily for 5 days with or without food.

Following oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure of nirmatrelvir was less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses (C4671001). Twice-daily dosing over 10 days achieved steady state on Day 2 with approximately 2-fold accumulation (C4671001). After a standardized FDA high-fat meal, the mean C_{max} and AUC of nirmatrelvir increased approximately 61% and 20%, compared to the fasted state, following administration of a 300 mg nirmatrelvir (2x 150 mg)/100 mg ritonavir tablets (C4671019).

Nirmatrelvir is extensively metabolized in vitro, and fraction metabolized by CYP3A4 was estimated to be 99% (084546 and 072016). In the presence of 100-mg ritonavir, the mean AUC and C_{max} of nirmatrelvir increased approximately 8- and 3.3-fold, respectively, confirming that nirmatrelvir is a sensitive CYP3A substrate (C4671001). Following coadministration of 300/100 mg nirmatrelvir/ritonavir twice daily with 200 mg itraconazole once daily, nirmatrelvir AUC and C_{max} increased 38.8% and 18.6%, respectively, suggesting that majority of the CYP3A pathway in nirmatrelvir elimination was blocked by ritonavir (C4671015). The results from the human ADME study, conducted with a single 300 mg nirmatrelvir co-administered with 100-mg ritonavir given at -12, 0, 12 and 24 hours relative to nirmatrelvir dosing, showed that approximately 49.6% and 35.3% of radioactivity dose were recovered in the urine (46.7% unchanged parent) and the feces (23.3% unchanged parent), respectively and none of the metabolites formed in the in vitro metabolism studies were observed (C4671001).

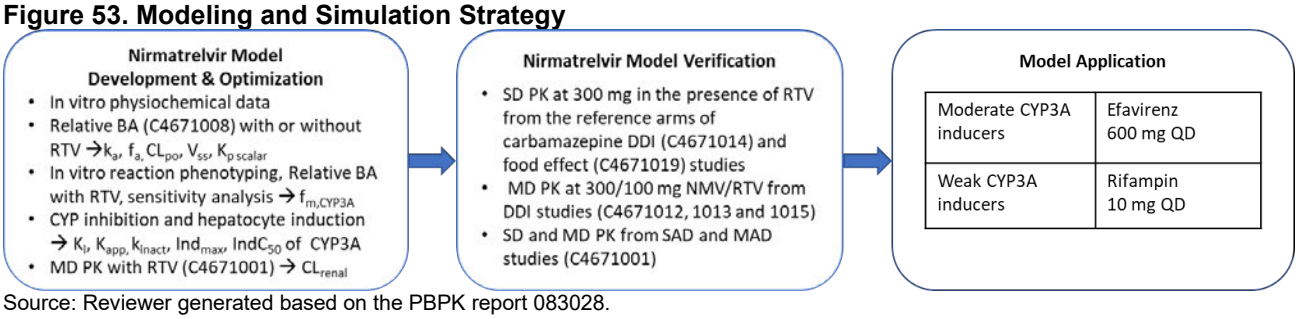
Based on in vitro drug interaction studies, nirmatrelvir is determined to be a competitive and time-dependent inhibitor and an inducer of CYP3A (Table 112). Nirmatrelvir is a substrate of P-gp, but not a substrate of BCRP, OATP1B1/3, OATP2B1, NTCP, OCT1/2, OAT1/2/3, MATE1/2K, PEPT1 and OATP4C1 (Study PF-07321332_24Nov20_114514 and_110227, Studies PF-07321332_23Jul21_124535, PF-07321332_14Jul21_013448, and PF-07321332_10Aug21_124557). Nirmatrelvir has low potential to inhibit various efflux and uptake

transporters except for P-gp and OATP1B1 (Table 112). In addition to the interaction studies with itraconazole and ritonavir, the Applicant conducted clinical DDI studies with carbamazepine (C4671014), dabigatran (C4671012) and midazolam (C4671013) to evaluate some of the in vitro findings. Refer to the Clinical Pharmacology review section for detail information on nirmatrelvir regarding ADME properties, in vitro and clinical studies used in the PBPK modeling.

Methods

Simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 21, Certara, Sheffield, UK). Schemes of the PBPK modeling and simulation strategy are shown in Figure 53, which summarizes the studies used for nirmatrelvir model development and verification, and model applications in predicting DDI with weak and moderate CYP3A inducers. The final model input parameters were summarized in Table 112. The nirmatrelvir PBPK model consists of a first-order absorption model, a full PBPK model (method 2) for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp library files ritonavir first-order compound file (SV-ritonavir_FO), itraconazole and metabolite (SV-Itraconazole_Fasted Soln and SV-OH-Itraconazole), carbamazepine and metabolite (SV-Carbamazepine and SV-Carbamazepine-10,11-epoxide), and midazolam (Sim-Midazolam) were used without any modification unless otherwise noted. Simulations were performed in a virtual healthy subject population (sim-Healthy Volunteers).

Figure 53. Modeling and Simulation Strategy



Source: Reviewer generated based on the PBPK report 083028.
Abbreviations: BA, bioavailability; CL_{renal}, renal clearance; CL_{po}, oral clearance; CYP, cytochrome P450; DDI, drug-drug interaction; f_a, fraction absorbed; $f_{m,CYP3A}$, fraction metabolized by CYP3A; IndC50, concentration at the half of maximal fold induction; Ind_{max}, maximum fold induction; k_a, absorption rate constant; K_i, reversible inh bition rate constant; k_{inact}, maximal enzyme inactivation rate constant measured for a time-dependent inhibitor; K_{app}, unbound inhibitor concentration at 50% k_{inact}; ; MAD, multiple ascending dose; MD, multiple dose; NMV, nirmatrelvir; PBPK, physiological-based pharmacokinetics; PK, pharmacokinetics; QD, once per day; RTV, ritonavir; SAD, single ascending dose; SD, single dose; V_{ss}, steady-state volume of distribution; K_p, tissue:plasma partition coefficients;

Table 112. Final Input Parameters in the Nirmatrelvir Model

Category	Parameters	Value	Reference
PhysChem Properties	MW	499.5	General Pharmaceutics Profile
	LogP	1.84	General Pharmaceutics Profile
	Compound type	Neutral	General Pharmaceutics Profile
	B/P	0.6	PF-07321332_18Nov20_100444
	f_{up}	0.31	PF-07321332_23Nov_010657
Elimination	$CL_{int,CYP3A4}$ (µl/min/pmol)	0.148	Retrograde with (b) (4) C4671008
	Additional HLM CL_{int} (µl/min/mg)	3.23	Retrograde with C4671008
	$f_{u,mic}$	1	Default
	CL_R (L/h)	3.4	C4671001 (Section 4.2)
Distribution	Kp Scalar	0.48	Parameter estimated with (b) (4) (C4671008) Full PBPK method 2
Absorption	k_a (h^{-1}) (b) (4)	2.63	Parameter estimation
	f_a (b) (4)	1	Assumed
	k_a (h^{-1}) (tablet)	0.55	Parameter estimation
	f_a (tablet)	0.73	C4671008 (Section 4.1)
	$f_{u,gut}$, Q_{gut} (L/h)	1, 10	Default
CYP3A4 Interaction	K_i (µM)	22.6	PF-07321332_04Nov_1139907
	K_{app} (µM)	13.9	PF-07321332_09Nov20_122202
	k_{inact} (h^{-1})	0.99	
	Ind_{max} (fold)	9.74	PF-07321332_18Oct20_102559 (Lot BNA, calibrated with rifampin)
	IndC50 (µM)	19.04	
	γ	1.63	
Transporter Interaction	Gut Apical P-gp K_i (µM)	55.2	PF-07321332_18Nov20_020944
	Gut Apical OCT1 K_i (µM)	138.1	
	Liver Sinusoidal OATP1B1 K_i (µM)	44.4	
	Liver Sinusoidal OATP1B3 K_i (µM)	283.2	
	Liver Sinusoidal OCT1 K_i (µM)	138.1	
	Liver Canalicular P-gp K_i (µM)	55.2	
	Liver Canalicular MATE1 K_i (µM)	111.7	
	Kidney Apical P-gp K_i (µM)	55.2	
	Kidney Apical MATEs Ki (µM)	111.7	
	Kidney Basal OCT2 K_i (µM)	954.5	
	Kidney Basal OAT3 K_i (µM)	520.6	

Source: Table 1 in PF-07321332_31May22_083028
Abbreviations: f_a, fraction absorbed; IndC50, concentration at the half of maximal fold induction; Ind_{max}, maximum fold induction; k_a, absorption rate constant; K_i, reversible inhibition rate constant; k_{inact}, maximal enzyme inactivation rate constant measured for a time-dependent inh bitor; K_I, unbound inh bitor concentration at 50% k_{inact}; $f_{u,gut}$, unbound fraction escaping gut metabolism; f_{up}, unbound fraction in the plasma; $f_{u,mic}$, unbound fraction in the microsomal incubation; B/P, blood to plasma concentration ratio; CL_{int}, intrinsic clearance; CL_R, renal clearance; MW, molecular weight; LogP, octanol-water partition coefficient; HLM, human liver microsome; Q_{gut}, nominal blood flow in the small intestine; K_p, tissue:plasma partition coefficients; (b) (4).

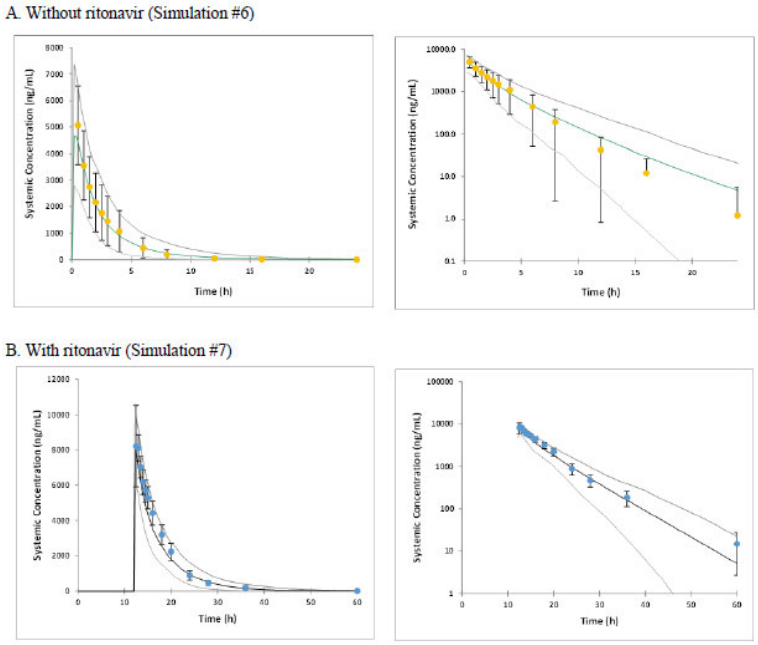
Results

Can the PBPK Model Adequately Describe the PK Profiles of Nirmatrelvir?

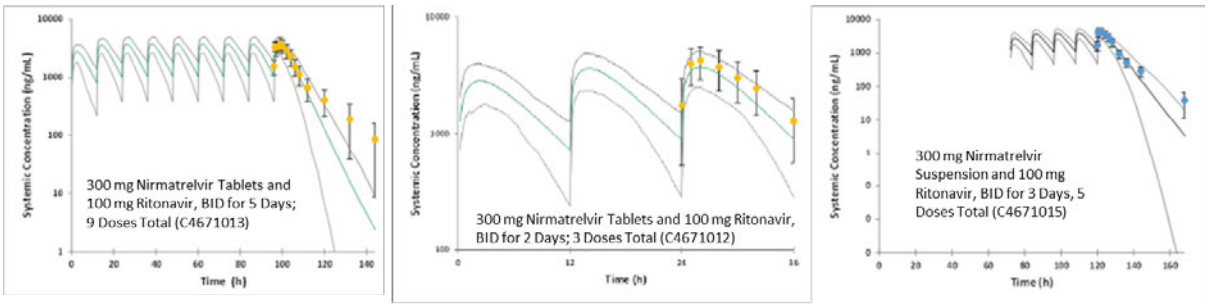
Yes. The nirmatrelvir PBPK model could reasonably well describe the PK of nirmatrelvir when ritonavir was present. Simulated and observed nirmatrelvir PK profiles and parameters following administration of single and multiple doses of 300/100 mg nirmatrelvir/ritonavir and different doses of nirmatrelvir co-administered with 100 mg ritonavir are summarized in Figure 54 and Table 113.

Figure 54. Simulated and Observed Nirmatrelvir PK Profiles Following Oral Administration of Single and Multiple Doses of Nirmatrelvir in Healthy Subjects

(A) Single Dose of 300 mg Nirmatrelvir (b) (4) Suspension Formulation Without or With Three Doses of 100 mg Ritonavir at -12, 0 and 12h



(B) Multiple Doses of Nirmatrelvir/Ritonavir (300/100 mg) Twice Daily



Source: (A) Figure 1 in the PBPK report 083028. (B) Figures 3 - 5 in the PBPK report 083028.
Note: In (A) Observed data from C4671008 the green and black line represents the predicted mean concentration the gray lines represent 5th and 95th percentile' the colored circles represent data points from participants. Vertical lines represent standard deviation.
Note: In (B) Depicted are simulated (lines) and observed data (circles). The green or black lines represent the mean data of the simulated population, and the grey lines represent 5% and 95% percentiles. Error bars represent standard deviation.
Abbreviations: BID, twice daily; PBPK, physiological-based pharmacokinetics; PK, pharmacokinetics

Table 113. Simulated and Observed PK Parameters Following Oral Administration of Single and Multiple Doses of Nirmatrelvir/Ritonavir in Healthy Subjects

Simulation purposes	Dosing Regimen	Observed		Simulated		Simulated/Observed		Clinical studies
		C_{max} ng/mL	AUC_{inf} ng•h/mL	C_{max} ng/mL	AUC_{inf} ng•h/mL	C_{max}	AUC_{inf}	
Model development	Nirmatrelvir (b) (4)	4871	10580	4670	11111	0.96	1.05	C4671008
	NMV (b) (4) 300 mg SD+ RTV 100 mg q12h, 3 doses	8840	48680	8157	42399	0.92	0.87	C4671008
	NMV (tablet) 300 mg SD+ RTV 100 mg q12h, 3 dose	3347	35540	3260	31348	0.97	0.88	C4671008
Model verificaton	NMV (tablet)/RTV 300/100 mg SD	3696	36810	3404	33226	0.92	0.90	C4671019
	NMV (tablet)/RTV 300/100 mg q12h, 5 days	3875	30680	3815	29129	0.98	0.95	C4671013
	NMV (tablet)/RTV 300/100 mg q12h, 3 doses	4065	30080	3788	28707	0.93	0.95	C4671012
	NMV (suspension)/RTV 300/100 mg q12h, 5 doses	4678	33350	3921	30611	0.84	0.92	C4671015
	NMV (tablet)/RTV 300/100 mg SD	2210	23010	2768	25527	1.25	1.11	C4671014

Source: Tables 5 and 6 in the PBPK report 083028.
Note: Geometric means are reported.
Abbreviations: AUC_{inf}, area under the concentration-time curve to infinity; C_{max}, maximum plasma concentration; NMV, nirmatrelvir; q12h, every 12 hours; PBPK, physiological-based pharmacokinetics; RTV, ritonavir; SD, single dose; (b) (4) suspension formulation

Can PBPK Analyses Predict the Effects of CYP3A Inducers on the PK of Nirmatrelvir?

The ritonavir model used by the Applicant is inadequate to predict the effects of CYP3A inducers on the exposure of nirmatrelvir/ritonavir combination. The reviewer developed and verified an alternative ritonavir model for this intended purpose. The reviewer's analysis predicted that weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ritonavir combination product. The reviewer's assessment is detailed below.

FDA's Assessment

Nirmatrelvir is predominantly metabolized by CYP3A. The main function of the ritonavir component in PAXLOVID is to boost the plasma exposure of nirmatrelvir through its strong inhibitory effect on CYP3A enzyme. The clinical DDI study with carbamazepine showed that the strong CYP3A inducer carbamazepine decreased plasma AUC of ritonavir by 83% (C4671014), presumably via CYP3A induction because ritonavir is also a CYP3A substrate. Consequently, the plasma AUC of nirmatrelvir reduced by 55% (C4671014) due to decrease in CYP3A inhibition by ritonavir and increase in CYP3A-mediated elimination of nirmatrelvir. Therefore, besides evaluating the adequacy of the nirmatrelvir PBPK model, whether the ritonavir PBPK model could reproduce the effects of CYP perpetrators on ritonavir will be one of the key factors to determine the adequacy of the modeling analysis for predicting effects of moderate and weak CYP3A inducers on nirmatrelvir exposure in the nirmatrelvir/ritonavir product.

Ritonavir PBPK Model

The default SV-ritonavir_FO model the Applicant used has not been verified for its use as a victim of DDI. FDA requested the Applicant to (1) demonstrate the ability of the ritonavir model could adequately simulate the ritonavir PK profiles and exposure at different doses, especially doses lower than 100 mg, following administration of single- and multiple-dose of ritonavir, and (2) simulate the DDI studies with itraconazole (C4671015) and carbamazepine (C4671014) to verify that the PBPK models of nirmatrelvir and ritonavir could simulate the observed effects of

CYP3A perpetrators on nirmatrelvir and ritonavir, respectively (FDA information request issued on December 13, 2022).

The simulation results are summarized in Table 114, Table 115 and Figure 55. Ritonavir exposure was reasonably well predicted for the doses ranging from 100 mg to 300 mg, but its exposure was underpredicted for doses above 400 mg and was overpredicted for doses less than 100 mg (Table 114). Therefore, the nonlinear PK of ritonavir was not well characterized by the default SV-ritonavir_FO model. Moreover, PBPK analyses could not reproduce the results from the carbamazepine DDI study. The PBPK simulation overpredicted ritonavir plasma concentrations and underpredicted the effect of carbamazepine on ritonavir exposure following co-administration of nirmatrelvir/ritonavir with carbamazepine (Table 115 and Figure 55). As a result of overprediction of ritonavir exposure, minimal effects of carbamazepine on nirmatrelvir PK were predicted, which is inconsistent with the 55% reduction in nirmatrelvir AUC observed in the study (C4671014). Therefore, the default SV-ritonavir_FO model was considered not suitable for predicting the effects of CYP3A inducers on ritonavir as a booster in a combination product.

Table 114. Simulated and Observed Ritonavir Exposure Following Single or Multiple Doses of Ritonavir

Ritonavir Dosing Regimen	Observed mean		Simulated mean		Simulated / Observed		References of observed data	Sources of simulated results
	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max}	AUC		
20 mg SD	44.7	235	63.5	461	1.42	1.96	PMID: 23381882	Tables 9 and 10 in PBPK report 083028
50 mg SD	94	862	164	1651	1.74	1.92		
50 mg QD 11 days [a]	257	2650	334	3466	1.30	1.31	PMID: 29302721	
100 mg BID 5 doses [b]	1440	7185	978	7550	0.68	1.05	C4671015	
100 mg SD [b]	359	3599	446	4338	1.24	1.21	C4671014	
20 mg QD 10 days [c]	20	134	111	930	5.71	6.94	PMID: 18815591	Reviewer's analysis
50 mg QD 10 days [c]	130	1120	362	3399	2.78	3.03		
100 mg QD 10 days [c]	807	6530	818	7904	1.01	1.21		
200 mg QD 10 days [c]	2460	16000	1734	17131	0.70	1.07		
100 mg BID 16 days	890	6200	1073	8966	1.21	1.45	PMID: 16338282	
200 mg BID 16 days	2300	17100	2216	18538	0.96	1.08	PMID: 9145841	
300 mg BID 16 days	3200	22600	3371	28335	1.05	1.25		
400 mg BID 16 days	7400	48400	4533	38217	0.61	0.79		
500 mg BID 16 days	11500	79900	5700	48162	0.50	0.60		

Source: PBPK report 083028, Reviewer's independent analysis and literature references(details in the table).
Note: AUC = $AUC_{0\text{-}inf}$ for SD. AUC_{24h} for QD. AUC_{12h} for BID.
[a.] Co-administered with venetoclax.
[b.] Co-administered with nirmatrelvir.
[c.] Co-administered with elvitegravir.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PBPK, physiological-based pharmacokinetics; PMID, PubMed unique identifier; QD, once per day; SD, single dose

Table 115. Geometric Means of Simulated and Observed PK Parameters of Ritonavir and Nirmatrelvir in the Presence of Carbamazepine

Paxlovid	$C_{max,ind}$ (ng/mL)	$AUC_{0\text{-}inf,\ ind}$ (ng*h/mL)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	Trials
Ritonavir				(b) (4)	Observed Simulated Sim/obs

Paxlovid	$C_{max,ind}$ (ng/mL)	$AUC_{0\text{-}inf,\ ind}$ (ng*h/mL)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	Trials
Nirmatrelvir	(b) (4)				Observed Simulated Sim/obs

Source: Applicant's response to FDA IR (seq0105) simulation output files c4671014-cbz-300mg-bid-plv-300mg-sd.xlsx, c4671014-control-plv-300mg-sd.xlsx.
Note: For carbamazepine DDI, carbamazepine was given orally 100 mg BID from Days 1 -3, 200 mg BID from Days 4 -7 and 300 mg BID from Days 8 -15, and a single dose of nirmatrelvir/ritonavir 300/100 mg was given on Day 14. Ind, in the presence of carbamazepine.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve to infinity; $AUC_{0\text{-}inf,ind}$, area under the concentration-time curve to infinity during induction; BID, twice daily; C_{max}, maximum plasma concentration; $C_{max,ind}$, maximum plasma concentration during induction; DDI, drug-drug interaction; Ind, induction; PK, pharmacokinetic Sim, simulated

Figure 55. Simulated and Observed PK Profiles of Ritonavir and Nirmatrelvir in the Presence of Carbamazepine

(b) (4)

Source: Applicant's response to FDA IR (seq0105), simulation output file c4671014-cbz-300mg-bid-plv-300mg-sd.xlsx
Note: Depicted are simulated (lines) and observed data (circles). The green lines represent the mean data of the simulated population (n = 120), and the grey and black lines represent 5% and 95% percentiles, respectively. Error bars represent standard deviation.
Abbreviations: log, logarithm; n, number of subjects in sample; PK, pharmacokinetic

Nirmatrelvir PBPK Model

The intrinsic clearance of CYP3A in the nirmatrelvir model was optimized by using sensitivity analysis of $f_{m,\ CYP3A}$ to recover the nirmatrelvir PK in the presence and absence of a single dose of 100 mg ritonavir in the relative bioavailability study (C4671008, Figure 54 and Table 113). However, ritonavir not only strongly inhibits CYP3A but also increases the AUC of fexofenadine, a P-gp substrate, up to 2.2-fold following a single dose of 100 mg ritonavir (PubMed 16809801). Nirmatrelvir is a substrate of both CYP3A and P-gp. Thus, the differences observed in nirmatrelvir PK in the presence and absence of ritonavir in the abovementioned study could be the net effect of ritonavir inhibition and/or induction on CYP3A and P-gp. The

Applicant performed verification of the nirmatrelvir model using multiple clinical studies (Table 113 and data from the PBPK report 074428 not shown), but these verifications were considered insufficient because all nirmatrelvir PK were simulated in the presence of 100 mg ritonavir. At this dose, ritonavir almost completely inhibits CYP3A activity rendering the contribution of CYP3A to the elimination of nirmatrelvir minimal (C4671001).

Despite insufficient verification of $f_{m, CYP3A}$ in the nirmatrelvir PBPK model, the model may still be useful for estimating the effects of CYP3A inducers on nirmatrelvir exposure because the current $f_{m, CYP3A}$ determination may be a conservative estimate as all the effects of ritonavir on nirmatrelvir was attributed to CYP3A inhibition. To test this possibility, the reviewer used this nirmatrelvir model to simulate the effect of carbamazepine on nirmatrelvir exposure by using the ritonavir exposure observed in the presence of carbamazepine. The ritonavir exposure was simulated using the SV-ritonavir-FO model with the following modifications. The "In Vivo Clearance model" was used for its elimination model, instead of "Enzyme kinetics model", and the clinically observed value of oral clearance of ritonavir (=16.4 L/h) was applied for the dose of 100-mg ritonavir (Mathias et al. 2010). This 'modified ritonavir model' could reproduce the observed ritonavir exposure following multiple-dose administration of 100-mg ritonavir and the effects of ritonavir on intravenous (IV) and oral midazolam. The predicted values were mostly within the bioequivalent bounds of the observed values (Table 116). This 'modified ritonavir model' was considered verified for the intended purpose, thus used for subsequent simulations. To simulate the effect of carbamazepine, ritonavir dose was reduced from 100 mg to 9 mg so that the simulated AUC of ritonavir matched the observed ritonavir AUC of 596.4 ng*h/mL in the presence of carbamazepine. This was needed since the mechanistic effect of CYP3A induction on ritonavir elimination was not considered in the modified ritonavir model. The simulations reasonably well reproduced the effects observed in the carbamazepine DDI study (Table 117), therefore the nirmatrelvir/modified ritonavir models could be used to estimate the effects of moderate CYP3A inducers on nirmatrelvir exposure.

Table 116. Prediction of Ritonavir Exposure and the Effects of Ritonavir on IV and Oral Midazolam PK Using the Modified SV-Ritonavir-FO Model

Dosing Regimens	PK Parameters	Ritonavir Exposure			Midazolam AUC or C_{max} Ratio		
		Observed	Predicted	Pred./Obs.	Observed	Predicted	Pred./Obs.
RTV 100 mg QD 10d + 1 mg *MDZ IV* D10	AUC (mg*h/L)	6.53	6.77	1.04	6.8	6.62	0.97
	C_{max} (mg/L)	0.807	0.75	0.93	1	1	1
RTV 100 mg BID 3d + 5 mg *MDZ PO* D3	AUC (mg*h/L)	6.2	6.77	1.09	23.9	27.1	1.13
	C_{max} (mg/L)	0.89	0.9	1.01	4.03	4.94	1.23

Source: Reviewer's analyses.
Note: Mean values are reported. Observed data from Aarnoutse et al. and Mathias et al.; Simulations were performed using SV-ritonavir-FO_in vivo CL (Aarnoutse et al. 2005; Mathias et al. 2010).
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CL, clearance; C_{max}, maximum plasma concentration; d or D, day; FO, first-order absorption; IV, intravenous; MDZ, midazolam; Obs, observed; PK, pharmacokinetic; PO, oral; Pred, predicted; QD, once per day; RTV, ritonavir..

Table 117. Simulated Effects of Carbamazepine on Nirmatrelvir in the Presence of Carbamazepine Following a Single Dose of PAXLOVID

Treatment	Control		Carbamazepine		Ratio		
Nirmatrelvir PBPK Model	C_{max} (ng/mL)	AUC (ng*h/mL)	$C_{max,inh}$ (ng/mL)	$AUC_{0-inf, inh}$ (ng*h/mL)	C_{max}	AUC_{0-inf}	Trials
Full model	2210	23010	1256	10240	0.57	0.45	observed
	3009	27708	1907	14085	0.63	0.51	simulated
	1.36	1.20	1.52	1.38	1.11	1.13	Sim/obs
Full model with no CYP3A inhibition parameters	2998	27562	1829	12449	0.61	0.45	Simulated
	1.36	1.20	1.46	1.22	1.07	1.00	Sim/obs
Full model with CYP3A IndC50/10 but no CYP3A inhibition parameters	2979	26873	1776	11305	0.60	0.42	Simulated
	1.35	1.17	1.41	1.10	1.05	0.93	Sim/obs
Full model with CYP3A IndC50/100 but no CYP3A inhibition parameters	2959	25291	1713	9655	0.58	0.38	Simulated
	1.34	1.10	1.36	0.94	1.02	0.85	Sim/obs

Source: Reviewer's analyses.
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-inf}, area under the concentration-time curve to infinity; $AUC_{0-inf,inh}$, area under the concentration-time curve to infinity during inhibition; C_{max}, maximum plasma concentration; $C_{max,inh}$, maximum plasma concentration during inhibition; CYP, cytochrome P450; $IndC_{50}$, concentration at the half of maximal fold induction; Obs, observed; Sim, simulated

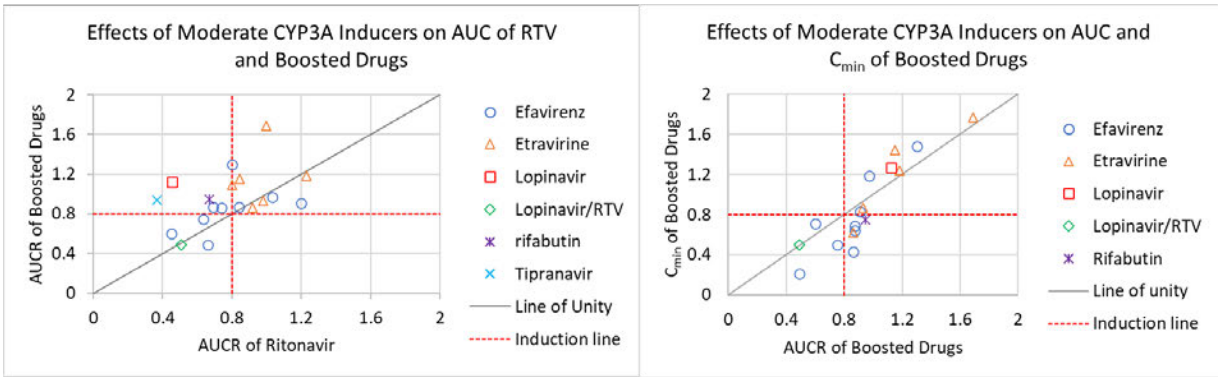
Model Application: Estimation of the Effects of Moderate CYP3A Inducers on Nirmatrelvir Exposure

The reviewer collected and analyzed publicly available data of clinical DDI studies of moderate CYP3A inducers with ritonavir-boosted anti-infective products. Figure 56 summarizes the effects of known moderate CYP3A inducers on the exposure of the components in ritonavir combinations. The maximal reduction in the AUC of ritonavir was 63%. In most cases, lesser reduction was observed in AUCs of the corresponding boosted drugs. The trough concentrations (C_{min}) of the boosted drugs, which are often the more relevant PK metrics to the efficacy of these anti-infectives, were more vulnerable to the induction than their AUCs. Whether a moderate CYP3A inducer reduces the C_{min} of the boosted drugs may depend on the dose of each co-administered components, the combination of co-administered components, and drug interaction potentials of the boosted drugs.

To simulate the effects of moderate CYP3A inducers on nirmatrelvir exposure, the reviewer reduced the dose of ritonavir of the 'modified ritonavir model' from 100 mg to 37 mg so that the AUC of ritonavir was reduced by 63%, the maximal reduction in ritonavir AUC observed so far. Moderate CYP3A inducers were predicted to have little effects on nirmatrelvir PK (Table 118), assuming ritonavir AUC was reduced up to 63% by moderate CYP3A inducers. As mentioned above, reduction in the C_{min} of the boosted drugs depends on drug interaction potentials of the boosted drugs. Nirmatrelvir is a time-dependent inhibitor and an inducer of CYP3A in vitro. The DDI potential of nirmatrelvir alone as a perpetrator of CYP3A has not been well characterized because its effect on midazolam was only evaluated together with 100-mg ritonavir. Therefore, the CYP3A inhibition and induction parameters in the nirmatrelvir model have not been sufficiently verified. To explore the effects of these CYP3A interaction parameters on the prediction, the reviewer performed additional simulations using the nirmatrelvir model but with the following modifications: (1) no CYP3A inhibition parameters (2) no CYP3A inhibition

parameters and the CYP3A induction parameter $IndC_{50}$ reduced by 10-fold (3) no CYP3A inhibition parameters and the CYP3A induction parameter $IndC_{50}$ reduced by 100-fold. These simulations examine the potential underprediction of the effects of moderate CYP3A inducers due to overprediction of CYP3A inhibition and underprediction of CYP3A induction by nirmatrelvir. The modified nirmatrelvir models (1) and (2) could reasonably well reproduce nirmatrelvir PK both following coadministration of carbamazepine with a single dose of nirmatrelvir/ritonavir 300/100 mg (C4671014) (Table 117) and following nirmatrelvir/ritonavir 300/100 mg twice daily for 5 days (C4671015) (Table 118). Using the same modified models, minimal changes were predicted on nirmatrelvir exposure when nirmatrelvir/ ritonavir 300/100 mg are co-administered with moderate CYP3A inducers (Table 118), confirming the previous predicted results. Based on these data, little changes are expected for weak CYP3A inducers.

Figure 56. Effects of Moderate CYP3A Inducers on the Exposure of the Components in Ritonavir Combinations



Source: Reviewer's analysis.
Abbreviations: AUCR, area under the concentration-time curve ratio; C_{min}, minimum plasma concentration; CYP3A, cytochrome P450, family 3, subfamily A; RTV, ritonavir

Table 118. Predicted Effects of Moderate CYP3A Inducers on Nirmatrelvir Exposure Following 5 Days of PAXLOVID Twice Daily Assuming Ritonavir AUC is Reduced by 63%

Nirmatrelvir PBPK Model	Interaction State	C_{max} (ng/mL)	AUC_{tau} (ng*h/mL)	C_{min} (ng/mL)
Observed in Itraconazole DDI	Control	3875	30680	900
Full model	Control	3843	29258	927
	induced	3751	28250	854
	Induced/control	0.98	0.97	0.92
Full model except for no CYP3A inhibition parameters	Control	3839	29209	923
	induced	3722	27940	833
	Induced/control	0.97	0.96	0.90
Full model with CYP3A IndC50 reduced 10-fold but no CYP3A inhibition parameters	Control	3781	28507	869
	induced	3507	25408	676
	Induced/control	0.93	0.89	0.78
Full model with CYP3A IndC50 reduced 100-fold but no CYP3A inhibition parameters	Control	3686	27392	755
	induced	3224	22446	473
	Induced/control	0.87	0.82	0.63

Source: Reviewer's analysis.
Abbreviations: AUC, area under the concentration-time curve; AUC_{tau}, area under the concentration-time curve over dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CYP3A, cytochrome P450, family 3, subfamily A; DDI, drug-drug interaction; $IndC_{50}$, concentration at the half of maximal fold induction; PBPK, physiological-based pharmacokinetics

Conclusions

Weak and moderate CYP3A inducers are expected to have minimal effects on nirmatrelvir exposure in the nirmatrelvir/ ritonavir 300/100 mg product.

14.7. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Applicant's Protocol Synopsis for EPIC-HR

Title

An Interventional Efficacy And Safety, Phase 2/3, Double-Blind, 2-Arm Study To Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo In Nonhospitalized Symptomatic Adult Participants With Covid-19 Who Are At Increased Risk Of Progressing To Severe Illness.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness.

Objectives, Endpoints, and Estimands

Table 119. Objectives, Endpoints, and Estimands for EPIC-HR

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of PF-07321332/ ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	• The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

Source: EPIC-HR final protocol amendment 4.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; mAb, monoclonal antibodies; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Overall Design

Brief Summary

This phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized, symptomatic adult subjects with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible subjects with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region and whether subjects have received/are expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization.

Enrollment of subjects who have received/are expected to receive COVID-19 therapeutic mAb treatment is expected to be approximately 20% and will be limited to approximately 25% of subjects. Enrollment of subjects that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to a total of approximately 1000 subjects.

Number of Subjects

Approximately 3000 subjects will be randomly assigned to study intervention.

"Enrolled" means a subject's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A subject will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Subjects will be screened within 48 hours of randomization. Eligible subjects will receive PF-07321332 plus ritonavir or placebo orally q12h for 5 days. The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Data Monitoring Committee or Other Independent Oversight Committee

An independent, external data monitoring committee (E-DMC) will review unblinded data to ensure the safety of subjects on an ongoing basis throughout the duration of the study, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 subjects have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 subjects in the primary analysis set with evaluable data complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.
- Interim analysis: A planned interim analysis for efficacy and futility will be done after approximately 45% of participants in the modified intent-to-treat (mITT) analysis set complete the Day 28 assessments (i.e., 28 days after randomization).

Statistical Methods

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or dying during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of losses to follow-up and summarized graphically for each treatment group. The estimand is then the difference of the proportions in the 2 groups and its 95% CI will be presented as well as the associated Wald test. For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula. The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is [Var(SPF(28)) + Var(SPlacebo(28))]. Instead of dealing with S(ti) the log-log approach to CI will be used. The 95% CI will be computed for the estimate of L(t)= log(-log(S(t))), the log hazard function.

The above primary analysis will also be conducted for the planned interim analysis. Two-sided 95% CI (adjusted for the planned interim analysis) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

The estimate of required sample size is based on data from the BLAZE-1 phase 2/3 trial among participants with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and/or hospitalization at enrollment. During the 29-day period following enrollment, the proportion of placebo-treated subjects with a COVID-19-related hospitalization/emergency department visit was 7% in the phase 3 portion of the trial.

This trial is designed to have 90% statistical power to show a difference of 3.5% in the proportion of subjects hospitalized/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF-07321332/ritonavir versus placebo), using a 2-sided Type I error

rate of 5%. Based on the above study, the proportion of hospitalization/death in the placebo arm is assumed to be 7%.

For a 2-sample proportion test, the sample size needed to detect this difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomized subjects.

Enrollment of subjects who have received/are expected to received COVID-19 therapeutic mAb treatment is expected to be approximately 20% of subjects, and will be limited to approximately 25% of subjects. Enrollment of subjects that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25%, and will be limited to a total of approximately 1000 subjects. Assuming a 5% dropout rate, the total sample size for this study will be approximately 3000 subjects.

Study enrollment will be stopped after approximately 1717 subjects are available for the primary analysis.

The primary estimand is the difference in proportions of patients experiencing COVID-19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit
   - WOCBP may be enrolled
   - All fertile participants must agree to use a highly effective method of contraception
2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization
3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. The specified signs/symptoms for study entry include:
   - cough
   - shortness of breath or difficulty breathing
   - fever (documented temperature >38˚C [100.4˚F]) or subjective fever (e.g., feeling feverish), chills or shivering
   - fatigue (low energy or tiredness)
   - muscle or body aches
   - diarrhea (loose or watery stools)
   - nausea (feeling like you wanted to throw up)
   - vomiting (throw up)
   - headache
   - sore throat
   - stuffy or runny nose

4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
   - ≥60 years of age
   - Body mass index (BMI) >25
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes.
   - Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
     - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry
     - Has received treatment with biologics (e.g., infliximab, ustekinumab), immunomodulators (e.g., methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry
     - HIV infection with CD4 cell count <200 mm3 and a viral load less than 400 copies/mL
   - Chronic lung disease (if asthma, requires daily prescribed therapy)
   - Known diagnosis of hypertension
   - Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass
   - Type 1 or Type 2 diabetes mellitus
   - Chronic kidney disease (CKD) provided the participant does not meet Exclusion Criterion 5
   - Sickle cell disease
   - Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
   - Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
   - Medical-related technological dependence (e.g., CPAP [not related to COVID-19])
5. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of hospitalization for the medical treatment of COVID-19
2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator
3. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection

4. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
5. Receiving dialysis or have known renal impairment [i.e., eGFR <45 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula]
6. Known HIV infection with viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
7. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
8. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
9. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir
12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment
13. Has received or is expected to receive convalescent COVID-19 plasma
14. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit
15. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the long-term follow-up visit
16. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
17. Known prior participation in this trial or other trial involving PF-07321332
18. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2x ULN (≥3 X ULN for Gilbert's syndrome)

- eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
- Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention

19. Oxygen saturation of < 92% on room air obtained at rest within 24 hours prior to randomization

Note: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation

20. Females who are pregnant or breastfeeding
21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

15.2. Applicant's Protocol Synopsis for EPIC-SR

Title

An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized Symptomatic Adult Participants with COVID-19 who are at Low Risk of Progressing to Severe Illness.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic, adult participants with COVID-19 who are at low risk of progression to severe illness.

Objectives, Endpoints, and Estimands

Table 120. Objectives, Endpoints, and Estimands for EPIC-SR

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	• Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	• The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤3 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	• The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤5 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

Objectives	Endpoints	Estimands
• To compare PF-07321332/ritonavir versus placebo for COVID-19 related hospitalization and all-cause mortality in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 • Proportion of participants with death (all cause) through Week 24.	• The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment. • Not Applicable
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	• Not applicable.
• To compare PF-07321332/ritonavir versus placebo for COVID-19-related medical visits in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28. • Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization through Day 28.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.

Source: EPIC-SR protocol amendment 4.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Overall Design

Brief Summary

This Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized symptomatic adult subjects with COVID-19 who are at low risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible subjects with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 days versus >3 to 5 days).

Number of Participants

Approximately 1140 subjects will be randomly assigned to study intervention.

"Enrolled" means a subject, or his or her legally authorized representative, agrees to participate in a clinical study following completion of the informed consent process and screening. A subject will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Subjects will be screened within 48 hours before randomization. Eligible subjects will receive PF-07321332 plus ritonavir or placebo orally q12h for 5 days. The total study duration is up to 24 weeks, with study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Data Monitoring Committee or Other Independent Oversight Committee

An independent E-DMC will review unblinded data to ensure the safety of participants throughout the duration of the study, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 100 randomized subjects have completed through Day 10. Whether enrollment is paused for this review will depend on the successful completion of the EPIC-HR sentinel cohort (after approximately the first 60 randomized participants have completed through Day 10). If the EPIC-HR sentinel cohort safety review has successfully completed and no clinically significant safety signals have been identified prior to enrollment of the first 100 participants in EPIC-SR, the study will continue without pause. Otherwise, enrollment of EPIC-SR will be paused pending the E-DMC review of safety data. After review of the sentinel cohort in EPIC-SR, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.

- Proof-of-concept assessment: Viral load data when 25% (approximately 200 subjects in the primary analysis set with evaluable data) complete the Day 5 assessments. Enrollment will

not be paused during review of these data, but may be paused or stopped following E-DMC review.

- Formal interim analysis: A planned formal interim analysis for efficacy and sample size re-estimation will be done after approximately 45% of subjects complete the Day 28 assessments in the mITT analysis set.

Details of the E-DMC are specified in the E-DMC Charter.

Statistical Methods

The primary endpoint of this trial is the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28. Time to sustained alleviation of all targeted COVID-19 signs/symptoms will be summarized graphically using Kaplan-Meier plots for each of the treatment group. Log-rank test will be used to compare the difference in time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between treatment groups.

The estimate of required sample size is based on the primary endpoint, the difference in time to sustained alleviation of all targeted COVID-19 associated signs/symptoms between subjects who were treated ≤3 days after COVID-19 symptom onset, treated with PF-07321332/ritonavir compared to placebo. The sample size is calculated based on a 2-sample test-parallel design–log-rank test, assuming a 90% power, 2-sided test at alpha = 0.05, approximate accrual rate of 30 subjects per day, 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms (6 days for PF-07321332/ritonavir and 8 days for placebo i.e., a 25% reduction in time to sustained alleviation of all targeted COVID-19 signs/symptoms) based on Lilly-BLAZE-11 and assuming a 18% study discontinuation rate, the sample size of approximately 800 participants (approximately 515 events) will provide 90% power to detect that difference.

Allowing for approximately 30% of subjects with COVID-19 symptom onset >3 days, a sample size of approximately 1140 subjects will be enrolled for this study. Trial enrollment will stop when approximately 800 subjects with COVID-19 symptom onset ≤3 days are randomized.

The primary estimand is the difference between PF-07321332/ritonavir and placebo in median time (days) to sustained alleviation of all targeted signs and symptoms of COVID-19 through Day 28 in non-hospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤3 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit
   - WOCBP may be enrolled
   - All fertile participants must agree to use a highly effective method of contraception

2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization

Note: RT-PCR is the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein are allowed. The test result must be available to confirm eligibility. Subjects may be enrolled based on positive results of a rapid SARS-CoV-2 antigen test performed at screening.

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. The specified signs/symptoms for study entry include:
   - cough
   - shortness of breath or difficulty breathing,
   - fever (documented temperature >38˚C [100.4˚F]) or subjective fever (e.g., feeling feverish)
   - chills or shivering
   - fatigue (low energy or tiredness)
   - muscle or body aches
   - diarrhea (loose or watery stools)
   - nausea (feeling like you wanted to throw up)
   - vomiting (throw up)
   - headache
   - sore throat
   - stuffy or runny nose
4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has at least 1 characteristic or underlying medical condition (self-report is acceptable) associated with an increased risk of developing severe illness from COVID-19 including:

Note: Participants with these conditions who are fully vaccinated (as defined by local regulations and practices) against SARS-CoV-2 are considered to be at lower risk of developing severe disease and are therefore considered eligible.

   - ≥60 years of age
   - BMI >25
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
   - Chronic lung disease (if asthma, requires daily prescribed therapy)
   - Known diagnosis of hypertension
   - Cardiovascular disease, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass

- Type 1 or Type 2 diabetes mellitus
- CKD
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer, other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period
- Medical-related technological dependence (e.g., CPAP [not related to COVID-19])

2. Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
   - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry
   - Has received treatment with biologics (e.g., infliximab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry'
   - HIV infection with CD4+ cell count <200/mm3
3. History of hospitalization for the medical treatment of COVID-19
4. Current need for hospitalization or anticipated need for hospitalization within 48 hour after randomization in the clinical opinion of the site investigator
5. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection
6. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
7. Receiving dialysis or have known renal impairment
8. Known HIV infection with viral load >400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
9. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
10. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
11. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
12. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
13. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with

serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir

14. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
15. Has received or is expected to receive monoclonal antibody treatment or convalescent COVID-19 plasma
16. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit, except for participants with any of the underlying medical conditions specified in Exclusion criterion #1 who are fully vaccinated prior to study entry

Note: Fully vaccinated participants with underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 must not receive a SARS-CoV-2 vaccine booster between screening and the Day 34 visit

17. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the long-term follow-up visit. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
18. Known prior participation in this trial or other trial involving PF-07321332
19. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2 X ULN (≥3x ULN for Gilbert's syndrome)
    - eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention.

20. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization

Note: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation.

21. Females who are pregnant or breastfeeding
22. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

15.3. Applicant's Protocol Synopsis for EPIC-PEP

Title

A phase 2/3, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study To Evaluate The Safety And Efficacy Of 2 Regimens Of Orally Administered PF-07321332/Ritonavir In Preventing Symptomatic SARS-CoV-2 Infection In Adult Household Contacts Of An Individual With Symptomatic COVID-19.

Rationale

The purpose of this trial is to evaluate the efficacy and safety of PF-07321332/ritonavir as post-exposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

Objectives, Endpoints, and Estimands

Table 121. Objectives, Endpoints, and Estimands for EPIC-PEP

Objectives	Endpoints	Estimands
Primary		
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
Secondary		
• To describe the safety and tolerability of 5-day and 10-day regimens of PF-07321332/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness: • Proportion of participants with symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28.	• The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. • Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a negative or positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the duration and severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28. • Number of days of symptomatic SARS-CoV-2 infection through Day 28.	• Not applicable.
• To determine the PK of PF-07321332 in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable.
• To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with death (all-cause) through Day 38.	• Not applicable.
• To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time. Of the participants who have a positive RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28.	• Not applicable.

Objectives	Endpoints	Estimands
• To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of COVID-19 related medical visits through Day 28.	• Not applicable.

Source: EPIC-PEP protocol amendment 2.
Abbreviations: AE, adverse event; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; PK, pharmacokinetic; RT-PCR, real-time, reverse transcription-polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse event

Overall Design

Brief Summary

This phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study in approximately 2880 subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts of individuals who are symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19) will compare the efficacy of 2 regimens of PF-07321332/ritonavir versus placebo. Index cases may be participants in Phase 2/3 safety and efficacy studies of PF-07321332/ritonavir (EPIC-SR C4671002 EPIC-HR C4671005), but this is not required. Eligible participants for this study will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to treatment in 1 of 3 intervention groups.

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness and geographic region at screening.

Number of Participants

Assuming approximately 5% of subjects will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 subjects.

"Enrolled" means a subject, or his or her legally authorized representative, agrees to participate in a clinical study following completion of the informed consent process and screening. A subjects will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Eligible subjects for this study (EPIC-PEP C4671006) will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- PF-07321332/ritonavir q12h for 5 days followed by matching placebo q12h for 5 days
- PF-07321332/ritonavir q12h for 10 days
- Matching placebo for PF-07321332/ritonavir q12h for 10 days

Subjects will be screened within 24 hours before randomization. The total duration of the study is up to 42 days and includes screening, study intervention through Day 10, efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days].

Data Monitoring Committee or Other Independent Oversight Committee

An independent E-DMC will review unblinded data to ensure the safety of subjects on an ongoing basis throughout the duration of the study. In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 subjects have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.
- Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by the E-DMC after a prespecified accrual of subjects (i.e., before or at approximately 70% overall subjects have completed the Day 14 assessments with a minimum number of 24 subjects having symptomatic infection [mITT analysis set]).

Statistical Methods

For the primary efficacy analysis, GEE will be used to analyze the proportion of subjects with a negative RT-PCR result at baseline who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for each treatment group. Comparisons between 5-day regimen of PF-07321332/ritonavir versus placebo group and 10-day regimen of PF-07321332/ritonavir versus placebo group will be presented as risk reduction with 95% CIs based on GEE analysis.

Based on the results from Study C4671005, which showed PF-07321332/ritonavir treatment significantly reduced the risk of hospitalization or death from any cause by 89% compared with placebo in nonhospitalized symptomatic adult subjects with COVID-19 who were at increased risk of progression to severe disease when they were treated within 3 days of symptom onset, and the high relative risk reduction (approximately 80%) observed in Regeneron REGEN-COV post-exposure prophylaxis study, the risk reduction between PF-07321332/ritonavir group versus placebo group is assumed to be 70%. The symptomatic infection rate assumption in the placebo group is adjusted to 4% based on the observed seropositivity rate in this study and the impact of seropositivity on the incidence of primary endpoint events in the REGEN-COV post-exposure prophylaxis study where the incidence of symptomatic infection was 2% in subjects who were seropositive and 8% in those who were seronegative.

Among baseline RT-PCR negative subjects, assuming an 4% symptomatic infection rate in the placebo group, a 70% reduction in symptomatic infection (1.2% symptomatic infection rate) in the PF-07321332/ritonavir group (5-day and 10-day regimen), a sample size of 821 subjects per group (2463 subjects total) will provide approximately 90% power for each comparison between 5-day and 10-day regimens of PF-07321332/ritonavir group versus placebo group under a 2-sided type-1 error rate of 5%. Assuming approximately 5% of subjects with negative rapid antigen test at screening will have a positive RT-PCR result at baseline, and assuming an

approximately 10% dropout rate, the total sample size for this study will be approximately 2880 subjects.

An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an independent E-DMC after a prespecified accrual of subjects (i.e., before or at approximately 70% overall subjects have completed the Day 14 assessments with a minimum number of 24 subjects having symptomatic infection [mITT analysis set]).

Complete Eligibility Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit

   WOCBP may be enrolled
   All fertile participants must agree to use a highly effective method of contraception
2. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
3. Subjects who have a negative screening SARS-CoV-2 rapid antigen test result and who are asymptomatic household contacts (i.e., living in the same residence) of an individual who is symptomatic and recently tested positive for SARS-CoV-2 (i.e., index case: patient with symptomatic COVID-19). To be included in the study, subjects must be randomized within 24 hours of their negative SARS-CoV-2 rapid antigen test and within 96 hours of collection of the index case's first positive SARS-CoV-2 test.

Note: The index case will have confirmation of SARS-CoV-2 infection by RT-PCR or other molecular or antigen tests that detect viral RNA or protein.

Note: Subjects with a negative screening SARS-CoV-2 local rapid antigen test result and whose baseline RT-PCR result is returned as positive would be allowed to remain on treatment in the study.

Note: Asymptomatic is defined as having no signs/symptoms consistent with COVID-19 and symptomatic is defined as having at least 1 of the specified signs or symptoms consistent with COVID-19 (cough, shortness of breath or difficulty breathing, fever with documented temperature >38˚C or subjective fever, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose, loss of smell, loss of taste).

4. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of SARS-CoV-2 infection as determined by a molecular test (antibody, antigen, or nucleic acid) from any specimen collected within 6 months before or during the screening visit

2. Experiencing measured fever (documented temperature >38˚C or 100.4˚F) or other signs or symptoms consistent with COVID-19
3. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure
4. CKD or have known moderate to severe renal impairment
5. Known HIV infection with viral load >400 copies/mL within the last 6 months or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit)
6. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention
7. Active cancer requiring treatment, with prohibited medication that must be administered/continued during the trial period
8. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator
9. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study
11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir
12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
13. Has received approved, authorized, or investigational anti-SARS-CoV-2 mAb, convalescent plasma, other drugs for treatment of COVID-19, or other anti-SARS-CoV-2 biologic products within 6 months of screening
14. Has received any SARS-CoV-2 vaccine (includes any level of vaccination) within 6 months prior to screening or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational post-exposure prophylaxis treatments through Day 38
15. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the End of Study visit
16. Previous administration with an investigational drug within 30 days (or as determined by local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer)
17. Known prior participation in this trial or other trial involving PF-07321332.

18. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5x ULN
    - Total bilirubin ≥2x ULN (≥3x ULN for Gilbert's syndrome).
    - eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula
    - Absolute neutrophil count <1000/mm3

Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention.

19. Females who are pregnant or breastfeeding
20. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members

16. Efficacy

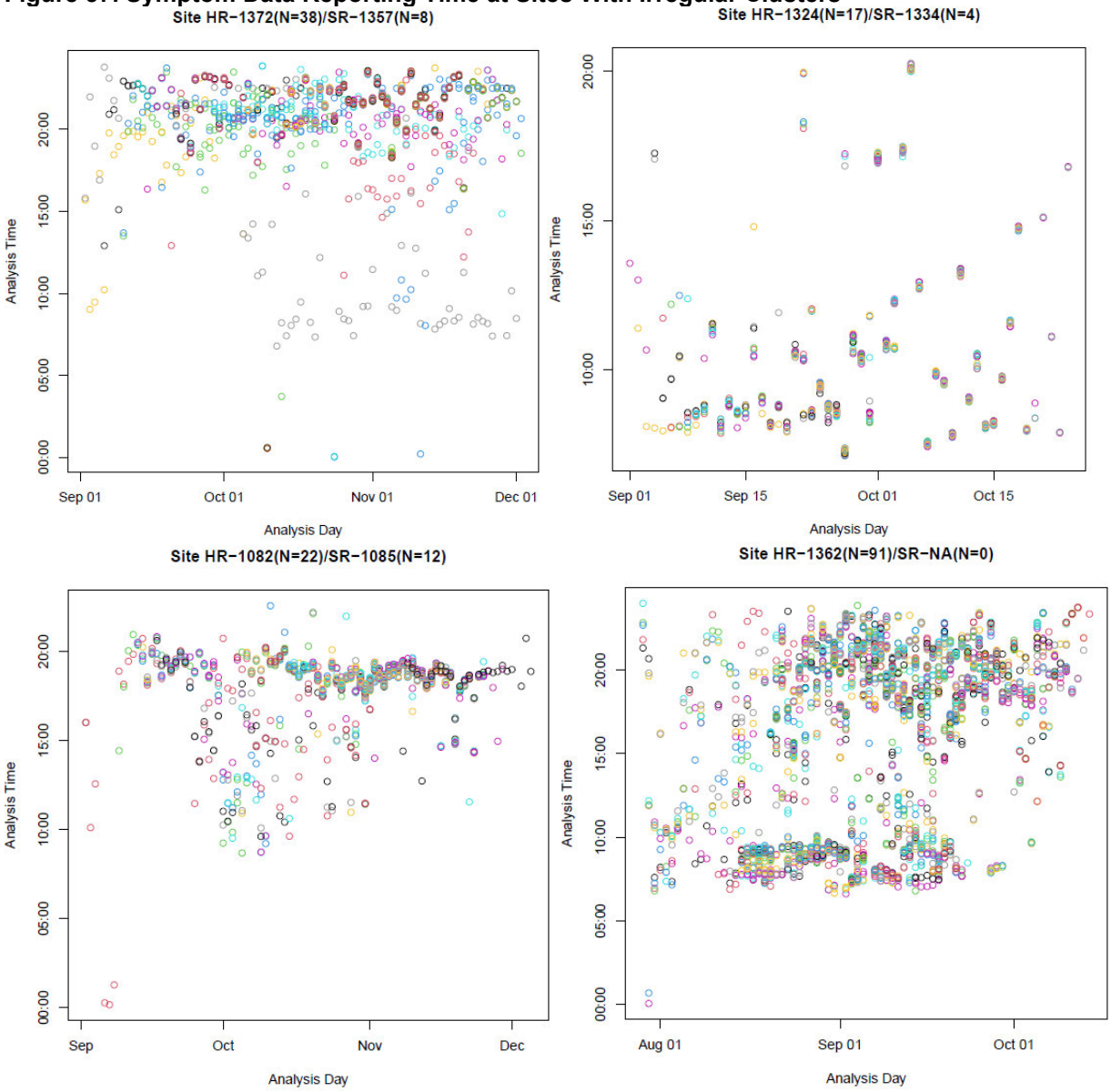
16.1. Sites With Abnormal Symptom Data Reporting Time Patterns

As discussed in Section 6.3.1, irregular symptom data reporting time clusters were observed at site HR1274/SR1281. Similar issues in symptom data with less extremity were observed at other sites, where there were no similar viral RNA data anomalies.

After reviewing symptom reporting time plots for EPIC-HR, EPIC-SR, EPIC-HR and EPIC-SR combined, and EPIC-HR and EPIC-SR (2021) combined, a group of sites, in addition to site HR1274/SR1281, were observed with abnormal symptom data reporting time clusters. These sites include: HR1372/SR1357, HR1324/SR1334, HR1082/SR1085, HR1362, HR1318/SR1388, HR1163, HR1103/SR1107, HR1501/SR1521, HR1014/SR1013(2021), SR1575. Figure 57, Figure 58, and Figure 59 show their symptom data reporting time patterns.

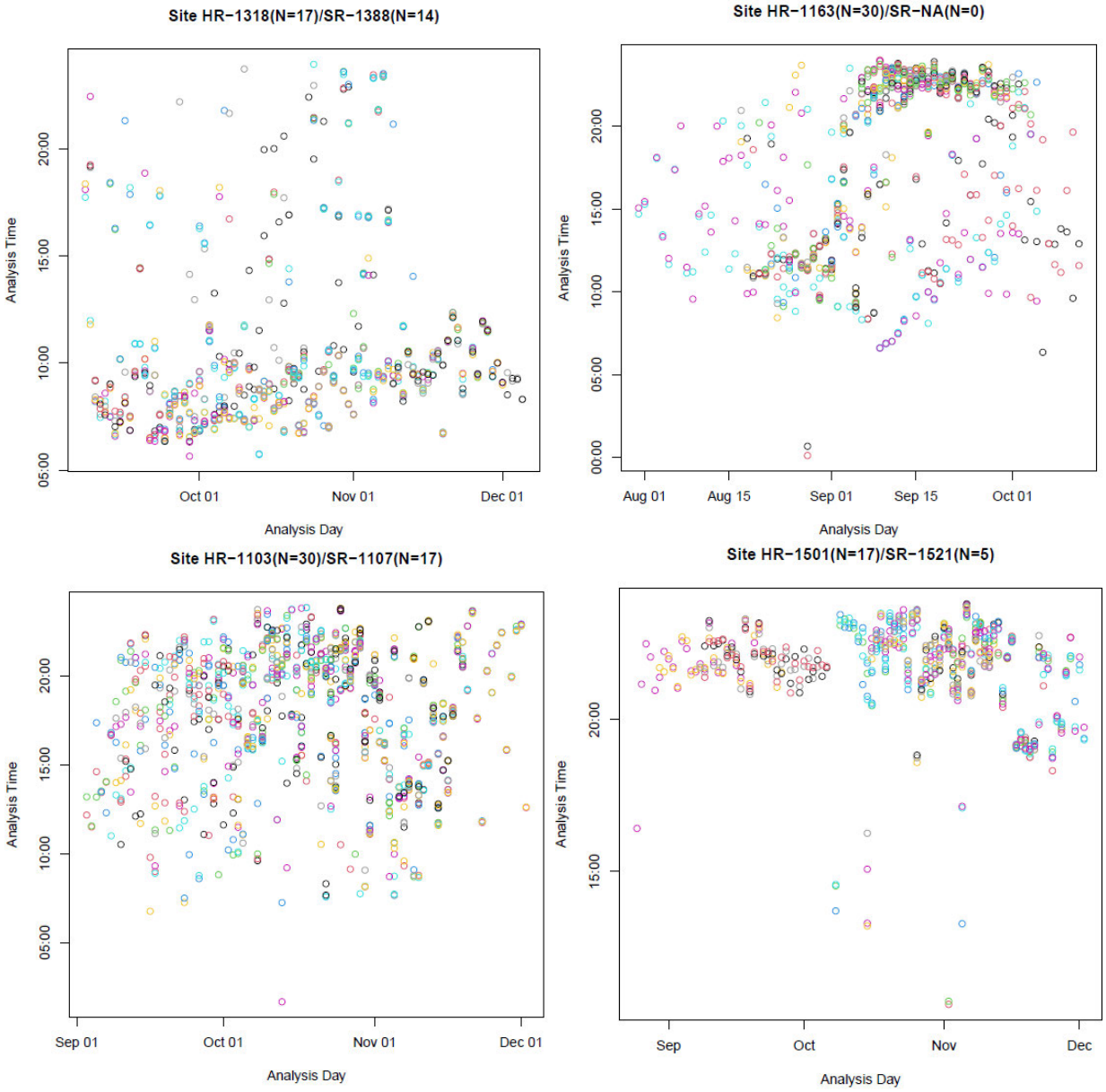
The Applicant conducted CluePoints analyses on two KRIs, SDOOG and SDOSG, for EPIC-HR, EPIC-SR, EPIC-SR (2021), EPIC-SR (2022), EPIC-HR and EPIC-SR combined, and EPIC-HR and EPIC-SR (2021) combined. All sites listed above expect HR1163 were flagged as medium risk or close to medium risk (i.e., HR1103/SR1107) in the Applicant's analyses of EPIC-HR and EPIC-SR (2021) combined and EPIC-SR (2022).

Figure 57. Symptom Data Reporting Time at Sites With Irregular Clusters



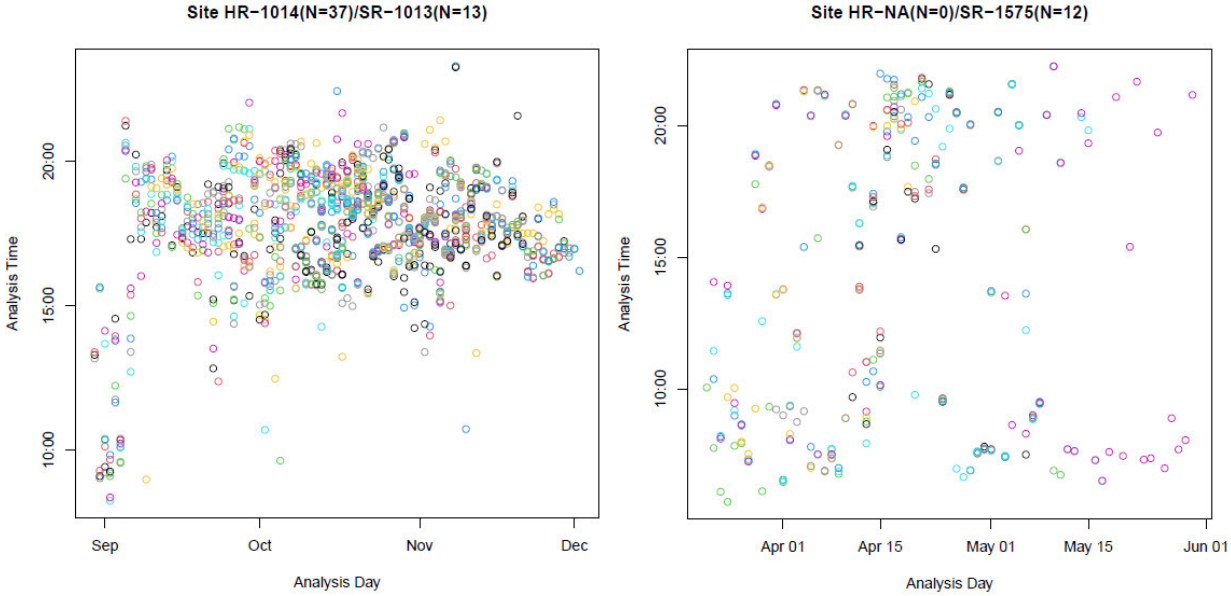
Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO dataset.
Abbreviations: N, total number of subjects

Figure 58. Symptom Data Reporting Time at Sites With Irregular Clusters (Continued)



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets
Abbreviations: N, total number of subjects

Figure 59. Symptom Data Reporting Time at Sites With Irregular Clusters (Continued)



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets
Abbreviations: N, total number of subjects

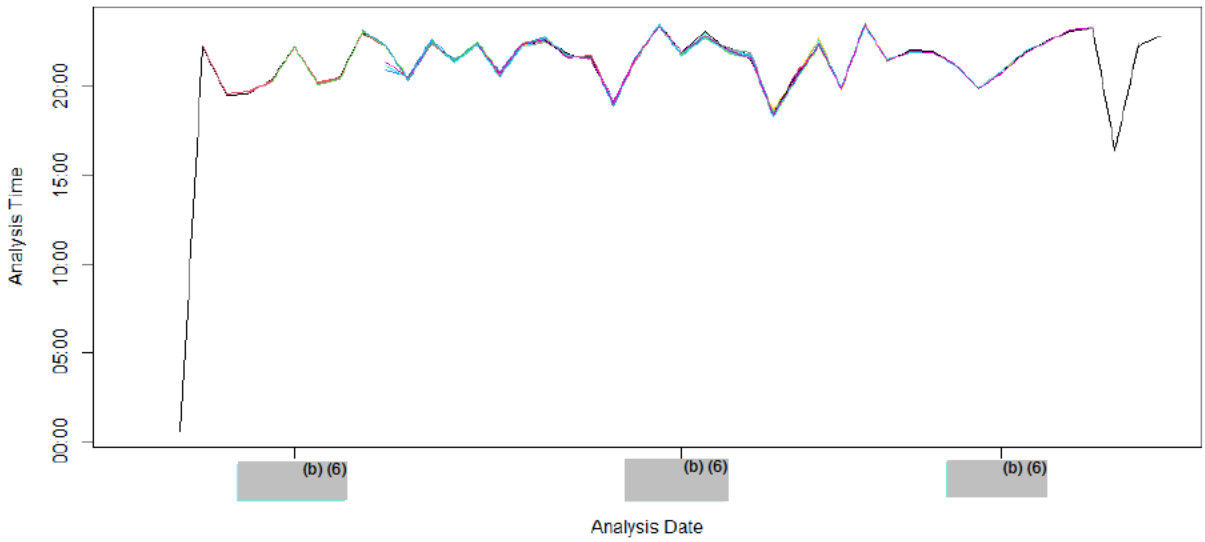
According to the Applicant, clustered data entry times may reflect individual site prescriptive instructions to subjects to ensure compliance. Subjects were provided guidance regarding selection of an easy to remember PIN code and reminder notifications for daily completion of the eDiaries at the same approximate time each day. If the COVID-19 Symptoms Diary was not completed prior to the first reminder being triggered, then 3 alarms sounded at 30-minute intervals. The permitted window for reminders to be sent was between 12:00 am and 10:30 pm. Subjects were able to use the App to change the reminder time on their own. Additionally, after the initial device set-up process, site staff had the ability to adjust the time that reminder notifications were sent to subjects to complete their COVID-19 Symptoms Diary each day. However, there are still patterns of clustered data entry times that cannot be explained by App reminder notifications.

Site HR1372/SR1357 and site HR1324/SR1334 had the highest ranks next to HR1274/SR1281 in the CluePoints analysis of EPIC-HR and EPIC-SR (2021) combined.

Figure 60 below displays symptom data reporting time for 14 subjects from site HR1372/SR1357 with ID in (b) (6) and (b) (6), who were enrolled between (b) (6), and (b) (6). Their symptom data reporting time were within approximately 10 minutes every day. At this site, 45 out of 47 subjects who had a PIN code shared the same PIN code of 3122.

According to the Applicant, subjects from this site were instructed select easy to remember PINs. Site staff provided example PINs but did not recall exact examples provided. Subjects with subject IDs (b) (6) through (b) (6) all have the same daily eDiary reminder time of 22:30. in addition to the reminders in the TrialMax application, study coordinators provided reminders to participants by phone at approximately the same time on a given day.

Figure 60. Symptom Data Reporting Time at Site HR1372/SR1357 for Subjects With IDs Within the Range of (b) (6) or (b) (6)

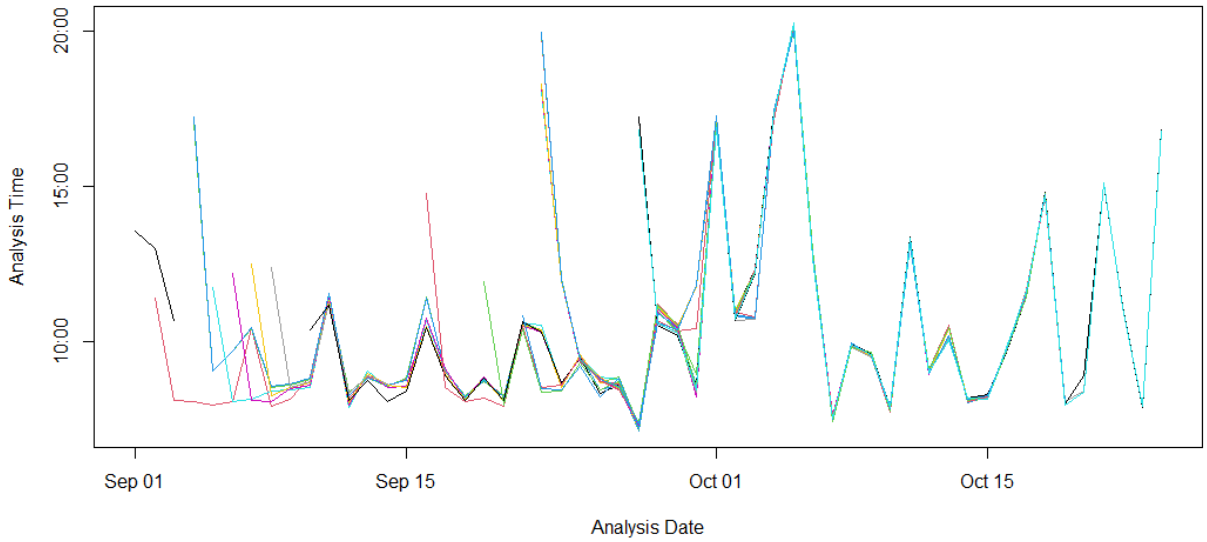


Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets.
Abbreviations: ID, identification

Figure 61 below displays symptom data reporting time for all subjects from site HR1324/SR1334. Almost all subjects have very similar symptom reporting time every day. All 21 subjects shared the same PIN code of 2252. A high percentage of subjects reporting resolution of all targeted symptoms after Day 1 was observed at this site, which is rare compared to other sites or sites from the same country.

According to the Applicant, all subjects from this site needed to stay in field hospital for quarantine 10-14 days per government policy. The coordinator reminded subjects in person to complete diary during14 days while subjects were in quarantine. After at home, subjects were reminded to complete eDiary via phone.

Figure 61. Symptom Data Reporting Time at Site HR1324/SR1334



Source: Reviewer's analysis on EPIC-HR and EPIC-SR ADSO datasets.

The following additional sensitivity analyses were conducted to evaluate the impact of certain sites with potential misconduct of symptom diary data collection, for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28, in mITT, mITT1, and mITT2 populations of study EPIC-HR. Similar to the primary efficacy analyses in Section 6, sites 1274 and 1470 were also excluded. Results were consistent with the primary analysis findings as provided in Table 122, Table 123, and Table 124.

- Sites with abnormal symptom data reporting time patterns in EPIC-HR were excluded. These sites include: 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163
- Sites with the shared PIN code issue (after combining EPIC-HR and EPIC-SR 2021 subjects by investigator, >50% subjects used the same PIN code and ≥10 subjects were enrolled) in EPIC-HR were excluded. These sites include: 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1274, 1276, 1030
- Sites with shared PIN code issue (as defined above) or with birth year PIN code issue (after combining EPIC-HR and EPIC-SR 2021 subjects by investigator, >50% subjects used birth year as PIN code and ≥10 subjects were enrolled, with the exception of site 1066, which has = 50%) in EPIC-HR were excluded. These sites include: 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1274, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066. Note that subjects' birth years were collected in the trial, while birth months and days were not.

Table 122. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Abnormal Symptom Data Reporting Time Patterns, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=573**	**N=546**
Participants with event, n (%)	4 (0.7)	42 (7.7)
COVID-19 hospitalization	4 (0.7)	42 (7.7)
Death	0	8 (1.5)
Estimated difference in proportion % (95% CI)[d]	-7.1 (-9.5, -4.7)	
Two-sided nominal p-value	<0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=833**	**N=843**
Participants with event, n (%)	8 (1.0)	60 (7.1)
COVID-19 hospitalization	8 (1.0)	59 (7.0)
Death	0	11 (1.3)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-8.1, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT2[c]	**Paxlovid**	**Placebo**
Analysis	**N=892**	**N=900**
Participants with event, n (%)	9 (1.0)	62 (6.9)
COVID-19 hospitalization	9 (1.0)	61 (6.8)
Death	0	11 (1.2)
Estimated difference in proportion % (95% CI)[d]	-6.0 (-7.8, -4.2)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

Table 123. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Shared PIN Code Issue, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=467**	**N=441**
Participants with event, n (%)	3 (0.6)	27 (6.1)
COVID-19 hospitalization	3 (0.6)	27 (6.1)
Death	0	4 (0.9)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.9, -3.2)	
Two-sided nominal p-value	<0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=682**	**N=690**
Participants with event, n (%)	6 (0.9)	43 (6.2)
COVID-19 hospitalization	6 (0.9)	42 (6.1)
Death	0	7 (1.0)
Estimated difference in proportion % (95% CI)[d]	-5.5 (-7.4, -3.5)	
Two-sided nominal p-value	<0.0001	
mITT2[c]	**Paxlovid**	**Placebo**
Analysis	**N=740**	**N=748**
Participants with event, n (%)	7 (0.9)	45 (6.0)
COVID-19 hospitalization	7 (0.9)	44 (5.9)
Death	0	7 (0.9)
Estimated difference in proportion % (95% CI)[d]	-5.2 (-7.0, -3.3)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030.

[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.

[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.

[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

Table 124. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding Sites With Shared PIN Code Issue or Birth Year PIN Code Issue, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=378**	**N=353**
Participants with event, n (%)	2 (0.5)	19 (5.4)
COVID-19 hospitalization	2 (0.5)	19 (5.4)
Death	0	3 (0.8)
Estimated difference in proportion % (95% CI)[d]	-4.9 (-7.4, -2.4)	
Two-sided nominal p-value	0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=560**	**N=567**
Participants with event, n (%)	4 (0.7)	33 (5.8)
COVID-19 hospitalization	4 (0.7)	32 (5.6)
Death	0	6 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.2 (-7.3, -3.1)	
Two-sided nominal p-value	<0.0001	
mITT2[c]	**Paxlovid**	**Placebo**
Analysis	**N=613**	**N=616**
Participants with event, n (%)	5 (0.8)	35 (5.7)
COVID-19 hospitalization	5 (0.8)	34 (5.5)
Death	0	6 (1.0)
Estimated difference in proportion % (95% CI)[d]	-5.0 (-7.0, -3.0)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066.

[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.

[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.

[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.

[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic; PIN, personal identification number

The following sites in EPIC-SR also had the above-mentioned shared PIN code issue or birth year PIN code issue, when looked at 2021 and 2022 data separately or combined: 1367, 1153, 1306, 1138, 1575, 1197, 1157. However, these sites did not have EPIC-HR enrollment, with the exception of EPIC-SR 1197. No PIN issue was reported in the corresponding EPIC-HR site 1193 (n = 59).

16.2. EPIC-HR

16.2.1. Interim Analysis Results, EPIC-HR

As of the data cutoff (October 26, 2021),1361 subjects were included in the full analysis set in the interim analysis. The primary endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population who received treatment within 3 days of symptom onset. The event rates were 27/387 (7.0%) in the placebo

group, and 3/393 (0.8%) in the PAXLOVID group (Table 125). After accounting for premature study discontinuation by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID showed a 6.3% (95% CI: -9.0% to -3.6%; p<0.0001) absolute reduction, or 89.1% relative reduction compared to placebo. The reduction was statistically significant, at α-level of 0.002, which was pre-specified for the interim analysis. This analysis did not exclude those enrolled at site 1274 and site 1470.

Table 125. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Interim Analysis, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=393**	**N=387**
Participants with event, n (%)	3 (0.8)	27 (7.0)
COVID-19 hospitalization	3 (0.8)	27 (7.0)
Death	0	7 (1.8)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-9.0, -3.6)	
Two-sided p-value	<0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=617**	**N=620**
Participants with event, n (%)	6 (1.0)	41 (6.6)
COVID-19 hospitalization	6 (1.0)	41 (6.6)
Death	0	10 (1.6)
Estimated difference in proportion % (95% CI)[d]	-5.8 (-7.9, -3.6)	
Two-sided p-value	<0.0001	
mITT2[c]	**Paxlovid**	**Placebo**
Analysis	**N=672**	**N=677**
Participants with event, n (%)	7 (1.0)	43 (6.4)
COVID-19 hospitalization	7 (1.0)	43 (6.4)
Death	0	10 (1.5)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.5, -3.4)	
Two-sided nominal p-value	<0.0001	

Source: EUA 105 review. Data from site 1274 and site 1470 were not excluded.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 126 below displays the results in mITT and mITT1 after excluding site 1274 and site 1470. Treatment with PAXLOVID showed a 6.5% (95% CI: -9.3% to -3.7%; p<0.0001) absolute reduction in mITT.

Table 126. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Updated Interim Analysis in mITT and mITT1, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=380**	**N=374**
Participants with event, n (%)	3 (0.8)	27 (7.2)
COVID-19 hospitalization	3 (0.8)	27 (7.2)
Death	0	7 (1.9)
Estimated difference in proportion % (95% CI)[c]	-6.5 (-9.3, -3.7)	
Two-sided p-value	<0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=574**	**N=587**
Participants with event, n (%)	6 (1.0)	39 (6.6)
COVID-19 hospitalization	6 (1.0)	39 (6.6)
Death	0	10 (1.7)
Estimated difference in proportion % (95% CI)[c]	-5.7 (-7.9, -3.5)	
Two-sided p-value	<0.0001	

Source: Reviewer's analysis. Data from site 1274 and site 1470 were excluded.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.2.2. Primary Endpoint Sensitivity Analyses, EPIC-HR

The following sensitivity analyses were conducted for the endpoint of COVID-19 related hospitalization or death from any cause through Day 28, in mITT, mITT1, and mITT2 populations. Results were consistent with the primary analysis findings.

- For subjects who enrolled more than once in EPIC-HR C4671005 or enrolled in EPIC-HR C4671005 and in 1 or 2 other phase 2/3 nirmatrelvir/ritonavir studies, data from a duplicate subject's first enrollment within this study were included and data from a duplicate participant's subsequent enrollments were excluded
- Sites in India were excluded
- Subjects who were lost to follow up before Day 21 were hypothetically assumed to have experienced both COVID-19-related hospitalization and death in a worst-case scenario
- Subjects who did not complete Day 28 follow up and discontinued study treatment due to adverse event were hypothetically assumed to have experienced both COVID-19-related hospitalization and death in a worst case-scenario

Table 127. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, First Enrollment Sensitivity Analysis, EPIC-HR

mITT[a]	**Paxlovid**	**Placebo**
Analysis	**N=664**	**N=643**
Participants with event, n (%)	5 (0.8)	44 (6.8)
COVID-19 hospitalization	5 (0.8)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[d]	-6.2 (-8.3, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b]	**Paxlovid**	**Placebo**
Analysis	**N=969**	**N=985**
Participants with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[d]	-5.7 (-7.3, -4.0)	
Two-sided nominal p-value	<0.0001	
mITT2[c]	**Paxlovid**	**Placebo**
Analysis	**N=1029**	**N=1049**
Participants with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.0, -3.8)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 128. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Excluding India Sites, EPIC-HR

mITT[a] Analysis	Paxlovid N=615	Placebo N=593
Participants with event, n (%)	5 (0.8)	44 (7.4)
COVID-19 hospitalization	5 (0.8)	44 (7.4)
Death	0	9 (1.5)
Estimated difference in proportion % (95% CI)[d]	-6.7 (-8.9, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=887**	**Placebo N=897**
Participants with event, n (%)	9 (1.0)	64 (7.1)
COVID-19 hospitalization	9 (1.0)	63 (7.0)
Death	0	12 (1.3)
Estimated difference in proportion % (95% CI)[d]	-6.2 (-8.1, -4.4)	
Two-sided nominal p-value	<0.0001	
mITT2[c] Analysis	**Paxlovid N=944**	**Placebo N=956**
Participants with event, n (%)	10 (1.1)	66 (6.9)
COVID-19 hospitalization	10 (1.1)	65 (6.8)
Death	0	12 (1.3)
Estimated difference in proportion % (95% CI)[d]	-5.9 (-7.7, -4.2)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 129. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Lost to Follow-Up Before Day 21 as Events, EPIC-HR

mITT[a] Analysis	Paxlovid N=671	Placebo N=647
Participants with event, n (%)	24 (3.6)	58 (9.0)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-8.0, -2.8)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=977**	**Placebo N=989**
Participants with event, n (%)	44 (4.5)	95 (9.6)
Estimated difference in proportion % (95% CI)[d]	-5.1 (-7.4, -2.9)	
Two-sided nominal p-value	<0.0001	

mITT2[c] Analysis	Paxlovid N=1038	Placebo N=1053
Participants with event, n (%)	46 (4.4)	98 (9.3)
Estimated difference in proportion % (95% CI)[d]	-4.9 (-7.0, -2.7)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 130. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Treatment Discontinuation Due to Adverse Event and Lost to Follow-Up as Events, EPIC-HR

mITT[a] Analysis	Paxlovid N=671	Placebo N=647
Participants with event, n (%)	7 (1.0)	47 (7.3)
Estimated difference in proportion % (95% CI)[d]	-6.3 (-8.4, -4.1)	
Two-sided nominal p-value	<0.0001	
mITT1[b] Analysis	**Paxlovid N=977**	**Placebo N=989**
Participants with event, n (%)	14 (1.4)	69 (7.0)
Estimated difference in proportion % (95% CI)[d]	-5.6 (-7.4, -3.8)	
Two-sided nominal p-value	<0.0001	
mITT2[c] Analysis	**Paxlovid N=1038**	**Placebo N=1053**
Participants with event, n (%)	15 (1.4)	71 (6.7)
Estimated difference in proportion % (95% CI)[d]	-5.4 (-7.1, -3.7)	
Two-sided nominal p-value	<0.0001	

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
[d.] The estimated cumulative proportion of participants hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.2.3. Primary Endpoint Subgroup Analyses, EPIC-HR

Subgroup analyses were conducted in mITT, mITT1, and mITT2 populations. Treatment with PAXLOVID showed no inconsistent effect in any subgroup of participants.

Table 131. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	5/671 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Sex				
Female	2/333 (0.6)	13/310 (4.2)	-3.6 (-6.0, -1.2)	0.0031
Male	3/338 (0.9)	31/337 (9.2)	-8.4 (-11.7, -5.1)	<0.0001
Age Group				
<65	4/580 (0.7)	28/556 (5.0)	-4.4 (-6.4, -2.4)	<0.0001
≥65	1/91 (1.1)	16/91 (17.6)	-16.5 (-24.6, -8.4)	<0.0001
Race				
White	5/484 (1.0)	37/491 (7.5)	-6.6 (-9.1, -4.1)	<0.0001
Black or African American	0/31	0/15	0.0 (0.0, 0.0)	N.A.
Asian	0/89	4/83 (4.8)	-4.9 (-9.5, -0.2)	0.0404
Others	0/67	3/58 (5.2)	-5.2 (-10.9, 0.5)	0.0753
Region				
United States	1/229 (0.4)	6/213 (2.8)	-2.4 (-4.8, 0.0)	0.0506
Europe	4/249 (1.6)	28/252 (11.1)	-9.6 (-13.8, -5.4)	<0.0001
India	0/56	0/54	0.0 (0.0, 0.0)	N.A.
Rest of the World	0/137	10/128 (7.8)	-7.9 (-12.7, -3.2)	0.0010
BMI				
<25	1/143 (0.7)	5/132 (3.8)	-3.1 (-6.6, 0.5)	0.0876
25 to <30	2/291 (0.7)	22/296 (7.4)	-6.8 (-10.0, -3.7)	<0.0001
≥30	2/237 (0.8)	17/219 (7.8)	-7.1 (-10.9, -3.3)	0.0003
Baseline serology status[a]				
Negative	5/339 (1.5)	40/338 (11.8)	-10.6 (-14.3, -6.8)	<0.0001
Positive	0/327	4/301 (1.3)	-1.3 (-2.6, 0.0)	0.0441
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	0/219	1/201 (0.5)	-0.5 (-1.5, 0.5)	0.3161
≥4	5/433 (1.2)	40/428 (9.3)	-8.3 (-11.3, -5.4)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	3/428 (0.7)	21/425 (4.9)	-4.3 (-6.5, -2.1)	0.0002
≥7	2/224 (0.9)	20/204 (9.8)	-9.0 (-13.4, -4.7)	<0.0001
Number of Comorbidities				
0-1	2/540 (0.4)	26/503 (5.2)	-4.9 (-6.9, -2.8)	<0.0001
2-3	3/128 (2.3)	18/142 (12.7)	-10.3 (-16.4, -4.2)	0.0009
≥4	0/3	0/2	0.0 (0.0, 0.0)	N.A.
Cigarette Smoker[a]				
Yes	3/272 (1.1)	13/277 (4.7)	-3.6 (-6.4, -0.8)	0.0111
No	2/397 (0.5)	31/370 (8.4)	-8.0 (-11.0, -5.0)	<0.0001
Diabetes mellitus[a]				
Yes	0/75	7/77 (9.1)	-9.1 (-15.5, -2.7)	0.0055
No	5/595 (0.8)	37/570 (6.5)	-5.7 (-7.9, -3.6)	<0.0001
Immunosuppression[a]				
Yes	0/3	0/5	0.0 (0.0, 0.0)	N.A.
No	5/667 (0.7)	44/642 (6.9)	-6.2 (-8.3, -4.1)	<0.0001
Chronic lung disease[a]				
Yes	0/37	1/26 (3.8)	-4.0 (-11.7, 3.7)	0.3074
No	5/633 (0.8)	43/621 (6.9)	-6.2 (-8.3, -4.1)	<0.0001

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Hypertension[a]				
Yes	4/217 (1.8)	29/224 (12.9)	-11.2 (-16.0, -6.4)	<0.0001
No	1/453 (0.2)	15/423 (3.5)	-3.4 (-5.2, -1.5)	0.0003
Cardiovascular disorder[a]				
Yes	0/26	9/33 (27.3)	-27.3 (-42.5, -12.1)	0.0004
No	5/644 (0.8)	35/614 (5.7)	-5.0 (-7.0, -3.0)	<0.0001
Chronic kidney disease[a]				
Yes	0/3	0/1	0.0 (0.0, 0.0)	N.A.
No	5/667 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Device dependence[a]				
Yes	0/2	0/1	0.0 (0.0, 0.0)	N.A.
No	5/663 (0.8)	43/643 (6.7)	-6.0 (-8.1, -3.9)	<0.0001
HIV infection[a]				
Yes	0/0	0/0	N.A.	N.A.
No	5/670 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	5/670 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Neurodevelopmental disorder[a]				
Yes	0/1	0/1	0.00 (0.00, 0.00)	N.A.
No	5/669 (0.7)	44/646 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
Cancer[a]				
Yes	0/3	0/4	0.00 (0.00, 0.00)	N.A.
No	5/667 (0.7)	44/643 (6.8)	-6.2 (-8.3, -4.1)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

Table 132. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT1 Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	9/977 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Sex				
Female	4/492 (0.8)	25/484 (5.2)	-4.4 (-6.6, -2.3)	<0.0001
Male	5/485 (1.0)	39/505 (7.7)	-6.8 (-9.3, -4.3)	<0.0001
Age Group				
<65	8/853 (0.9)	45/865 (5.2)	-4.3 (-6.0, -2.7)	<0.0001
≥65	1/124 (0.8)	19/124 (15.3)	-14.6 (-21.2, -8.1)	<0.0001
Age Group				
≤60	8/804 (1.0)	36/783 (4.6)	-3.7 (-5.3, -2.0)	<0.0001
>60	1/173 (0.6)	28/206 (13.6)	-13.1 (-18.0, -8.3)	<0.0001
Race				
White	8/682 (1.2)	51/705 (7.2)	-6.1 (-8.3, -4.0)	<0.0001
Black or African American	0/44	1/31 (3.2)	-3.2 (-9.4, 3.0)	0.3094
Asian	1/146 (0.7)	6/149 (4.0)	-3.4 (-6.8, 0.1)	0.0560
Others	0/105	6/104 (5.8)	-5.9 (-10.6, -1.3)	0.0116

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Region				
United States	2/341 (0.6)	12/348 (3.4)	-2.9 (-5.0, -0.8)	0.0072
Europe	4/325 (1.2)	37/329 (11.2)	-10.2 (-13.8, -6.5)	<0.0001
India	0/90	0/92	0.0 (0.0, 0.0)	N.A.
Rest of the World	3/341 (0.6)	15/348 (4.3)	-5.6 (-9.3, -1.9)	0.0034
BMI				
<25	1/201 (0.5)	8/200 (4.0)	-3.5 (-6.4, -0.6)	0.0175
25 to <30	3/440 (0.7)	27/444 (6.1)	-5.5 (-7.9, -3.1)	<0.0001
≥30	5/336 (1.5)	29/345 (8.4)	-7.1 (-10.4, -3.8)	<0.0001
BMI				
<30	4/641 (0.6)	35/644 (5.4)	-4.9 (-6.7, -3.0)	<0.0001
≥30	5/336 (1.5)	29/345 (8.4)	-7.1 (-10.4, -3.8)	<0.0001
Duration since first symptom, days				
≤3	5/671 (0.7)	44/647 (6.8)	-6.1 (-8.2, -4.1)	<0.0001
>3	4/306 (1.3)	20/342 (5.8)	-4.6 (-7.4, -1.8)	0.0015
Baseline serology status[a]				
Negative	8/475 (1.7)	56/497 (11.3)	-9.8 (-12.9, -6.7)	<0.0001
Positive	1/490 (0.2)	8/479 (1.7)	-1.5 (-2.7, -0.3)	0.0179
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	1/342 (0.3)	2/352 (0.6)	-0.3 (-1.2, 0.7)	0.5772
≥4	8/607 (1.3)	59/610 (9.7)	-8.5 (-11.1, -6.0)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	7/676 (1.0)	35/706 (5.0)	-4.0 (-5.8, -2.2)	<0.0001
≥7	2/273 (0.7)	26/256 (10.2)	-9.6 (-13.5, -5.7)	<0.0001
Number of Comorbidities				
0-1	4/789 (0.5)	42/793 (5.3)	-4.9 (-6.5, -3.2)	<0.0001
2-3	5/184 (2.7)	22/194 (11.3)	-8.6 (-13.7, -3.5)	0.0009
≥4	0/4	0/2	0.0 (0.0, 0.0)	N.A.
Cigarette Smoker[a]				
Yes	5/381 (1.3)	16/400 (4.0)	-2.7 (-5.0, -0.5)	0.0184
No	4/594 (0.7)	48/589 (8.2)	-7.6 (-10.0, -5.3)	<0.0001
Diabetes mellitus[a]				
Yes	3/106 (2.8)	9/111 (8.1)	-5.3 (-11.3, 0.7)	0.0839
No	6/870 (0.7)	55/878 (6.3)	-5.7 (-7.4, -3.9)	<0.0001
Immunosuppression[a]				
Yes	0/6	0/6	0.0 (0.0, 0.0)	N.A.
No	9/970 (0.9)	64/983 (6.5)	-5.7 (-7.4, -4.0)	<0.0001
Chronic lung disease[a]				
Yes	0/56	2/33 (6.1)	-6.2 (-14.4, 2.1)	0.1445
No	9/920 (1.0)	62/956 (6.5)	-5.6 (-7.3, -3.9)	<0.0001
Hypertension[a]				
Yes	5/305 (1.6)	41/326 (12.6)	-11.1 (-15.0, -7.2)	<0.0001
No	4/671 (0.6)	23/663 (3.5)	-2.9 (-4.4, -1.4)	0.0002
Cardiovascular disorder[a]				
Yes	0/37	11/45 (24.4)	-24.4 (-37.0, -11.9)	0.0001
No	9/939 (1.0)	53/944 (5.6)	-4.7 (-6.4, -3.1)	<0.0001
Chronic kidney disease[a]				
Yes	0/5	0/7	0.0 (0.0, 0.0)	N.A.
No	9/971 (0.9)	64/982 (6.5)	-5.7 (-7.4, -4.0)	<0.0001

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Device dependence[a]				
Yes	0/3	0/1	0.0 (0.0, 0.0)	N.A.
No	9/963 (0.9)	63/980 (6.4)	-5.6 (-7.2, -3.9)	<0.0001
HIV infection[a]				
Yes	0/0	0/1	N.A.	N.A.
No	9/976 (0.9)	64/987 (6.5)	-5.7 (-7.3, -4.0)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	9/976 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Neurodevelopmental disorder[a]				
Yes	0/1	0/1	0.0 (0.0, 0.0)	N.A.
No	9/975 (0.9)	64/988 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Cancer[a]				
Yes	0/5	0/6	0.0 (0.0, 0.0)	N.A.
No	9/971 (0.9)	64/983 (6.5)	-5.7 (-7.4, -4.0)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

Table 133. Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 by Baseline Demographics, mITT2 Population, EPIC-HR

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Overall	10/1038 (1.0)	66/1053 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Sex				
Female	4/522 (0.8)	25/515 (4.9)	-4.1 (-6.2, -2.1)	0.0001
Male	6/516 (1.2)	41/538 (7.6)	-6.6 (-9.0, -4.1)	<0.0001
Age Group				
<65	9/909 (1.0)	47/919 (5.1)	-4.2 (-5.8, -2.6)	<0.0001
≥65	1/129 (0.8)	19/134 (14.2)	-13.5 (-19.6, -7.4)	<0.0001
Race				
White	9/728 (1.2)	53/756 (7.0)	-5.6 (-7.9, -3.8)	<0.0001
Black or African American	0/52	1/35 (2.9)	-2.9 (-8.4, 2.7)	0.3103
Asian	1/153 (0.7)	6/156 (3.8)	-3.2 (-6.5, 0.1)	0.0562
Others	0/105	6/106 (5.7)	-5.8 (-10.4, -1.3)	0.0116
Region				
United States	3/387 (0.8)	14/399 (3.5)	-2.8 (-4.8, -0.7)	0.0076
Europe	4/330 (1.2)	37/333 (11.1)	-10.0 (-13.7, -6.4)	<0.0001
India	0/94	0/97	0.0 (0.0, 0.0)	N.A.
Rest of the World	3/227 (1.3)	15/224 (6.7)	-5.5 (-9.2, -1.8)	0.0033
BMI				
<25	1/208 (0.5)	8/206 (3.9)	-3.4 (-6.2, -0.6)	0.0174
25 to <30	3/466 (0.6)	28/464 (6.0)	-5.5 (-7.8, -3.2)	<0.0001
≥30	6/364 (1.6)	30/383 (7.8)	-6.3 (-9.4, -3.3)	<0.0001
Duration since first symptom, days				
≤3	5/715 (0.7)	46/687 (6.7)	-6.1 (-8.1, -4.1)	<0.0001
>3	5/323 (1.5)	20/366 (5.5)	-4.0 (-6.7, -1.2)	0.0044
Baseline COVID-19 mAb treatment,				
Not received/expected	9/977 (0.9)	64/989 (6.5)	-5.6 (-7.3, -4.0)	<0.0001
Received/expected	1/61 (1.6)	2/64 (3.1)	-1.5 (-6.9, 3.8)	0.5756

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Baseline serology status[a]				
Negative	8/504 (1.6)	58/526 (11.0)	-9.6 (-12.6, -6.7)	<0.0001
Positive	2/521 (0.4)	8/514 (1.6)	-1.2 (-2.4, 0.0)	0.0538
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<4	2/358 (0.6)	2/374 (0.5)	0.0 (-1.0, 1.1)	0.9661
≥4	8/652 (1.2)	61/650 (9.4)	-8.3 (-10.8, -5.9)	<0.0001
Baseline Viral RNA (NP samples, log_{10} copies/mL)[a]				
<7	8/716 (1.1)	37/750 (4.9)	-3.9 (-5.6, -2.1)	<0.0001
≥7	2/294 (0.7)	26/274 (9.5)	-9.0 (-12.6, -5.3)	<0.0001
Number of Comorbidities				
0-1	5/843 (0.6)	44/844 (5.2)	-4.70 (-6.3, -3.1)	<0.0001
2-3	5/191 (2.6)	22/205 (10.7)	-8.10 (-12.9, -3.3)	0.0010
≥4	0/4	0/4	0.0 (0.0, 0.0)	N.A.
Cigarette smoker[a]				
Yes	5/397 (1.3)	16/418 (3.8)	-2.6 (-4.8, -0.4)	0.0186
No	5/639 (0.8)	50/635 (7.9)	-7.2 (-9.5, -5.0)	<0.0001
Diabetes mellitus[a]				
Yes	3/108 (2.8)	9/118 (7.6)	-4.9 (-10.6, 0.9)	0.0961
No	7/929 (0.8)	57/935 (6.1)	-5.4 (-7.1, -3.8)	<0.0001
Immunosuppression[a]				
Yes	0/6	0/7	0.0 (0.0, 0.0)	N.A.
No	10/1031 (1.0)	66/1046 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Chronic lung disease[a]				
Yes	0/60	2/38 (5.3)	-5.3 (-12.5, 1.9)	0.1462
No	10/977 (1.0)	64/1015 (6.3)	-5.4 (-7.0, -3.7)	<0.0001
Hypertension[a]				
Yes	5/318 (1.6)	42/346 (12.1)	-10.7 (-14.5, -6.9)	<0.0001
No	5/719 (0.7)	24/707 (3.4)	-2.7 (-4.2, -1.3)	0.0003
Cardiovascular disorder[a]				
Yes	0/39	11/47 (23.4)	-23.4 (-35.5, -11.3)	0.0002
No	10/998 (1.0)	55/1006 (5.5)	-4.5 (-6.1, -3.0)	<0.0001
Chronic kidney disease[a]				
Yes	0/5	0/7	0.0 (0.0, 0.0)	N.A.
No	10/1032 (1.0)	66/1046 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Device dependence[a]				
Yes	0/4	0/3	0.0 (0.0, 0.0)	N.A.
No	10/1023 (1.0)	65/1042 (6.2)	-5.3 (-6.9, -3.7)	<0.0001
HIV infection[a]				
Yes	0/0	0/1	N.A.	N.A.
No	10/1037 (1.0)	66/1051 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Sickle cell disease[a]				
Yes	0/0	0/0	N.A.	N.A.
No	10/1037 (1.0)	66/1053 (6.3)	-5.4 (-7.0, -3.8)	<0.0001

Demographic Parameters	Paxlovid n/N (%)	Placebo n/N (%)	Difference in % (95% CI)	Nominal p-value
Neurodevelopmental disorder[a]				
Yes	0/2	0/1	0.0 (0.0, 0.0)	N.A.
No	10/1035 (1.0)	66/1052 (6.3)	-5.4 (-7.0, -3.8)	<0.0001
Cancer[a]				
Yes	0/5	0/6	0.00 (0.00, 0.00)	N.A.
No	10/1032 (1.0)	66/1047 (6.3)	-5.4 (-7.0, -3.8)	<0.0001

Source: Reviewer's Analysis, excluding subjects from site 1274 and site 1470.
[a.] Those with missing baseline status were not included.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; log, logarithm; mAb, monoclonal ant bodies; mITT, modified intent to treat; N, total number of subjects; n, number of subjects in sample; N.A., not applicable; NP, nasopharyngeal; RNA, ribonucleic acid

16.2.4. Time to Sustained Alleviation and Resolution of Each Targeted Symptom, EPIC-HR

Time to sustained alleviation and time to sustained resolution for each targeted symptom were evaluated in the mITT, mITT1 and mITT2 populations. Numerical reduction in median time to sustained alleviation and median time to sustained resolution was observed in most symptoms. Cough usually lasted longer compared to other symptoms.

Table 134. Time to Sustained Symptom Alleviation of Each Targeted Symptom Through Day 28, EPIC-HR

	Paxlovid N=666			Placebo N=645		
Symptoms in mITT[a]	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	460	68	6	408	98	7
Shortness of Breath or Difficulty Breathing	230	47	6	227	63	8
Chills or Shivering	370	42	3	309	67	5
Cough	458	81	8	408	117	10
Diarrhea	142	23	4	120	23	4
Feeling Hot or Feverish	384	36	3	327	71	5
Headache	438	56	5	373	80	7
Nausea	191	30	4	178	42	5
Stuffy or Runny Nose	419	47	6	361	79	7
Sore Throat	339	34	5	288	59	6
Vomit	59	10	3	59	11	3

	Paxlovid N=970			Placebo N=986		
Symptoms in mITT1[b]	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	650	122	6	603	175	7
Shortness of Breath or Difficulty Breathing	351	72	6	335	116	8
Chills or Shivering	508	76	3	469	109	5
Cough	650	141	9	613	203	10
Diarrhea	224	38	5	200	46	4
Feeling Hot or Feverish	533	70	3	491	122	5
Headache	606	103	5	559	150	7
Nausea	289	59	5	287	76	6
Stuffy or Runny Nose	604	86	6	542	142	7
Sore Throat	481	67	5	447	113	6
Vomit	97	19	3	96	19	3

	Paxlovid N=1031			Placebo N=1050		
Symptoms in mITT2[c]	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)	Achieved Sustained Alleviation (n)	No Sustained Alleviation (n)	Median Time to Sustained Alleviation (Days)
Muscle or Body Aches	689	132	6	644	186	8
Shortness of Breath or Difficulty Breathing	381	78	6	359	128	9
Chills or Shivering	545	82	3	506	114	5
Cough	690	153	9	653	221	10
Diarrhea	244	43	5	226	50	4
Feeling Hot or Feverish	574	75	3	528	128	5
Headache	646	113	5	604	156	7
Nausea	308	66	5	310	80	6
Stuffy or Runny Nose	644	95	6	586	152	7
Sore Throat	510	72	5	488	119	6
Vomit	110	22	3	112	23	3

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470
Note: Median time to event calculated from Kaplan-Meier Estimate .
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibodies; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

Table 135. Time to Sustained Symptom Resolution of Each Targeted Symptom Through Day 28, Trial EPIC-HR

	Paxlovid N=666			Placebo N=645		
Symptoms in mITT[a]	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**
Muscle or Body Aches	410	118	9	361	145	12
Shortness of Breath or Difficulty Breathing	215	62	8	198	92	11
Chills or Shivering	360	52	5	290	86	7
Cough	415	124	13	348	177	15
Diarrhea	138	27	6	111	32	6
Feeling Hot or Feverish	374	46	5	308	90	7
Headache	405	89	8	334	119	11
Nausea	184	37	5	163	57	7
Stuffy or Runny Nose	383	83	9	325	115	10
Sore Throat	316	57	7	266	81	9
Vomit	59	10	3	59	11	3

	Paxlovid N=970			Placebo N=986		
Symptoms in mITT1[b]	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**	**Achieved Sustained Resolution (n)**	**No Sustained Resolution (n)**	**Median Time to Sustained Resolution (Days)**
Muscle or Body Aches	585	187	9	539	239	12
Shortness of Breath or Difficulty Breathing	325	98	9	288	163	12
Chills or Shivering	494	90	5	441	137	7
Cough	579	212	13	525	291	15
Diarrhea	220	42	6	185	61	6
Feeling Hot or Feverish	519	84	5	464	149	7
Headache	560	149	9	505	204	11
Nausea	276	72	7	269	94	7
Stuffy or Runny Nose	551	139	9	487	197	11
Sore Throat	448	100	7	416	144	9
Vomit	97	19	3	96	19	3

	Paxlovid N=1031			Placebo N=1050		
Symptoms in mITT2[c]	Achieved Sustained Resolution (n)	No Sustained Resolution (n)	Median Time to Sustained Resolution (Days)	Achieved Sustained Resolution (n)	No Sustained Resolution (n)	Median Time to Sustained Resolution (Days)
Muscle or Body Aches	621	200	9	578	252	12
Shortness of Breath or Difficulty Breathing	355	104	9	311	176	13
Chills or Shivering	531	96	5	476	144	7
Cough	615	228	13	563	311	15
Diarrhea	239	48	6	210	66	6
Feeling Hot or Feverish	560	89	5	498	158	7
Headache	598	161	9	547	213	11
Nausea	295	79	7	292	98	7
Stuffy or Runny Nose	589	150	9	527	211	11
Sore Throat	477	105	7	457	150	9
Vomit	110	22	3	112	23	4

Source: Reviewer's analysis, excluding subjects from site 1274 and site 1470.
[a.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset.
[b.] All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset.
[c.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset.
Note: Median time to event calculated from Kaplan-Meier Estimate.
Note: Participants with no symptom diary data were not included in the analyses.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibodies; mITT, modified intent to treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.3. EPIC-SR

16.3.1. Other Efficacy Endpoints, EPIC-SR

Table 136. Time to Sustained Symptom Resolution Through Day 28, EPIC-SR

Sustained Symptom Resolution in mITT1[a]	Paxlovid N=540	Placebo N=528
Participants with sustained symptom resolution, n (%)	347 (64.3)	345 (65.3)
Median time to sustained symptom resolution (95% CI)	15 (14, 16)	16 (15, 18)
Two-sided nominal p-value	0.4248	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from log rank test.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: CI, confidence interval; N, number of patients in treatment group; n, number of patients with given characteristic

Table 137. Proportion of Participants With Any Severe Targeted Signs and Symptoms Attributed to COVID-19 Through Day 28, EPIC-SR

mITT1[a] Analysis	Paxlovid N=534	Placebo N=527
Participants with event, n (%)	102 (19.1)	119 (22.6)
Two-sided nominal p-value	0.1629	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from Pearson's Chi-squared test.
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment group; n, number of patients with given characteristic

Table 138. Proportion of Participants With Progression to Worsening Status in 1 or More Self-Reported COVID-19-Associated Targeted Symptoms Through Day 28, EPIC-SR

mITT1[a] Analysis	Paxlovid N=534	Placebo N=527
Participants with event, n (%)	410 (76.8)	418 (79.3)
Two-sided nominal p-value	0.3181	

Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: p-values calculated from Pearson's Chi-squared test.
Note: Participants with no symptom diary data were not included in the analyses.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment group; n, number of patients with given characteristic

Table 139. Proportion of Participants With COVID-19-Related Medical Visits, EPIC-SR

Medical Visits in mITT1[a]	Paxlovid N=540	Placebo N=528
Participants with event, n (%)	12 (2.2)	23 (4.4)
Total number of medical visits across all participants	16	35
Two-sided nominal p-value	0.0740	

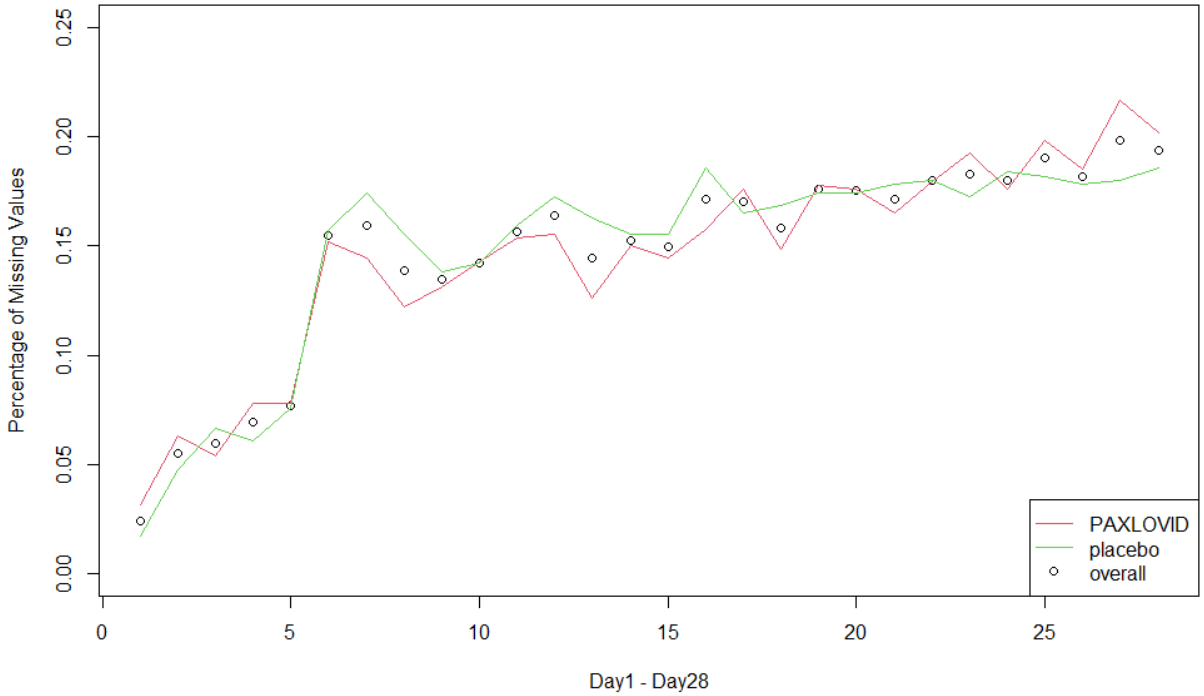
Source: Reviewer's analysis, excluding subjects from site 1281 and site 1488.
Note: Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19-Related-Hospitalization (ICU and non-ICU stays). The medical visits and hospitalization events are limited through Day 34 visit.
Note: p-values calculated from Pearson's Chi-squared test with continuity correction.
[a.] All participants randomly assigned to study intervention who took at least 1 dose of study intervention.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; N, number of patients in treatment group; n, number of patients with given characteristic

16.4. Additional Analyses on Symptom Diary Data

16.4.1. Symptom Diary Data Missing Values

In EPIC-HR, there was an average of 18.3% missing symptom diary entries (18.0% in PAXLOVID arm and 18.7% in placebo arm) in mITT2. Figure 62 below shows the missing data percentages on a daily basis. The missing data percentages on Days 1 through 5 were generally lower, as subjects were on treatment. The missing data percentages went up to around 20%-25% after Day 5. The missing data percentages were similar between two arms.

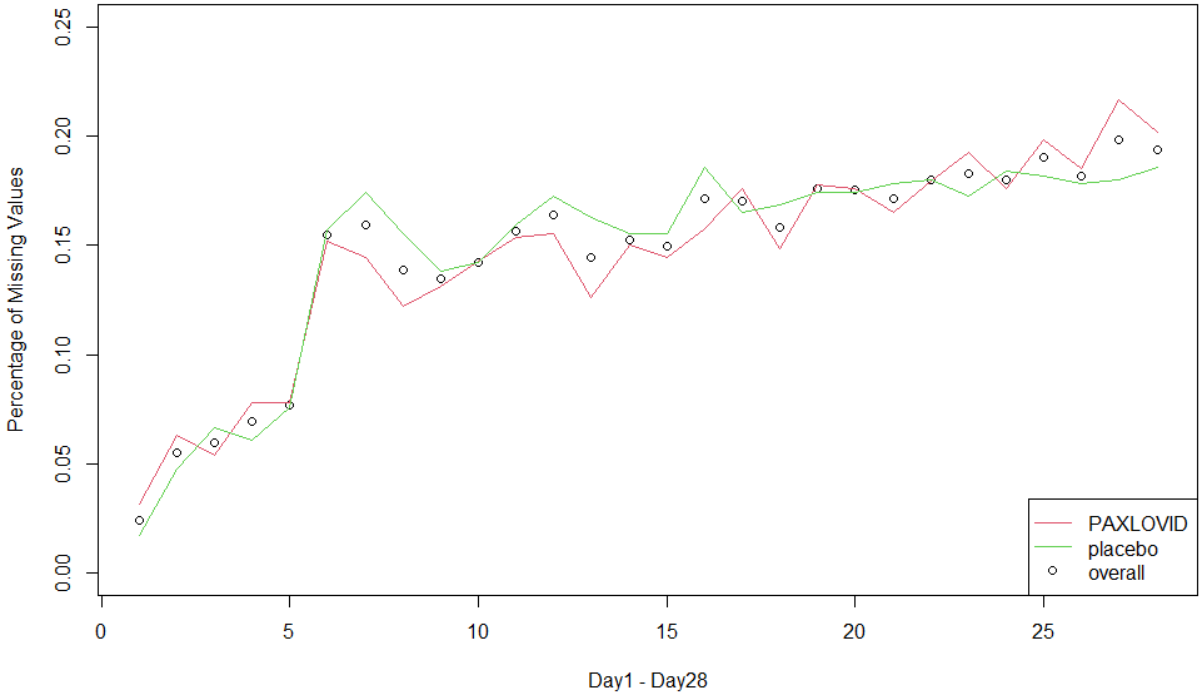
Figure 62. EPIC-HR Missing Symptom Diary Data



Source: Reviewer's analysis on EPIC-HR ADSO dataset.
Note: Data from site 1274 and site 1470 were excluded.

In EPIC-SR 2021, there was an average of 14.7% missing symptom diary entries (14.6% in PAXLOVID arm and 14.8% in placebo arm) in mITT1. Figure 63 below shows the missing data percentages on a daily basis. The missing data percentages on Days 1 through 5 were generally lower, as subjects were on treatment. The missing data percentages went up to around 15%-20% after Day 5. The missing data percentages were similar between two arms.

Figure 63. EPIC-SR 2021 Missing Symptom Diary Data



Source: Reviewer's analysis on EPIC-SR 2021 ADSO dataset.
Data from site 1281 and site 1488 were excluded.

16.4.2. Additional Symptom Rebound Analyses

Table 140 below presents symptom rebound analysis in EPIC-HR seropositive subgroup and EPIC-SR 2021 vaccinated high-risk subgroup. As found in the general analysis in Section 6.3.6, symptom rebound rates were similar in the PAXLOVID group and the placebo group.

Table 140. Symptom Rebound Analysis in Subgroups of Interest

Subgroup	Paxlovid	Placebo
EPIC-HR Seropositive, N	518	512
Short symptom recovery, n (%)[a]	404 (78.0)	381 (74.4)
Symptom rebound, n (%)[b]	41 (10.1)	42 (11.0)
Moderate symptom rebound, n (%)[b]	23 (5.7)	26 (6.8)
EPIC-SR 2021 Vaccinated High-risk, N	316	314
Short symptom recovery, n (%)[a]	246 (77.8)	243 (77.4)
Symptom rebound, n (%)[b]	41 (16.7)	36 (14.8)
Moderate symptom rebound, n (%)[b]	26 (10.6)	27 (11.1)

Source: Reviewer's analysis, excluding subjects from site HR1274/SR1281 and site HR1470/SR1488. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total N subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group

Table 141 presents symptom rebound analysis, excluding sites with abnormal symptom data reporting time patterns. Table 142 presents symptom rebound analysis, excluding sites with symptom data collection misconduct with respect to PIN codes. As found in the general analysis in Section 6.3.6, symptom rebound rates in PAXLOVID group were similar to or lower than the placebo group in both analyses.

Table 141. Symptom Rebound Analysis, Excluding Sites With Abnormal Symptom Data Reporting Time Patterns

Rebound Analysis	Paxlovid	Placebo
EPIC-HR, N	885	897
Short symptom recovery, n (%)[a]	630 (71.2)	565 (63.0)
Symptom rebound, n (%)[b]	82 (13.0)	91 (16.1)
Moderate symptom rebound, n (%)[b]	51 (8.1)	58 (10.3)
EPIC-SR 2021 (Pre-Omicron), N	494	494
Short symptom recovery, n (%)[a]	375 (75.9)	377 (76.3)
Symptom rebound, n (%)[b]	63 (16.8)	56 (14.9)
Moderate symptom rebound, n (%)[b]	40 (10.7)	40 (10.6)
EPIC-SR 2022 (Omicron), N	106	102
Short symptom recovery, n (%)[a]	89 (84.0)	84 (82.4)
Symptom rebound, n (%)[b]	7 (7.9)	9 (10.7)
Moderate symptom rebound, n (%)[b]	3 (3.4)	8 (9.5)

Source: Reviewer's analysis, excluding subjects from EPIC-HR sites 1470, 1274, 1501, 1324, 1362, 1014, 1372, 1082, 1318, 1103, 1163, and excluding subjects from EPIC-SR sites 1488, 1281, 1357, 1334, 1085, 1388, 1107, 1521, 1013 (2021), 1575. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group

Table 142. Symptom Rebound Analysis, Excluding Sites With Symptom Data Collection Issue With Respect to PIN Codes

Rebound Analysis	Paxlovid	Placebo
EPIC-HR, N	607	613
Short symptom recovery, n (%)[a]	432 (71.2)	383 (62.5)
Symptom rebound, n (%)[b]	62 (14.4)	60 (15.7)
Moderate symptom rebound, n (%)[b]	37 (8.6)	34 (8.9)
EPIC-SR 2021 (Pre-Omicron), N	312	328
Short symptom recovery, n (%)[a]	233 (74.7)	251 (76.5)
Symptom rebound, n (%)[b]	36 (15.5)	39 (15.5)
Moderate symptom rebound, n (%)[b]	22 (9.4)	30 (12.0)
EPIC-SR 2022 (Omicron), N	67	60
Short symptom recovery, n (%)[a]	52 (77.6)	44 (73.3)
Symptom rebound, n (%)[b]	5 (9.6)	9 (20.5)
Moderate symptom rebound, n (%)[b]	2 (3.8)	8 (18.2)

Source: Reviewer's analysis, excluding subjects from EPIC-HR sites 1470, 1274, 1309, 1062, 1492, 1153, 1076, 1324, 1034, 1163, 1318, 1082, 1372, 1014, 1097, 1158, 1362, 1325, 1276, 1030, 1219, 1155, 1273, 1442, 1382, 1399, 1395, 1058, 1135, 1501, 1331, 1374, 1037, 1149, 1066, and excluding subjects from EPIC-SR sites 1488, 1281, 1061, 1085, 1150, 1508, 1388, 1282, 1013, 1367, 1100, 1333, 1018, 1317, 1077, 1334, 1022, 1357, 1158, 1222, 1155, 1280, 1393, 1153, 1306, 1459, 1414, 1409, 1137, 1521, 1384, 1029, 1575, 1060, 1138, 1145, 1157, 1197. Subjects with no symptom data were not included in the analyses.
[a.] Percentage over total subjects.
[b.] Percentage over those who achieved short symptom recovery.
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group; PIN, personal identification number

16.5. Real-World Evidence on Effectiveness

16.5.1. Literature Review on PAXLOVID Effectiveness Real-World Evidence

16.5.1.1. Review Methods and Materials

The Division of Epidemiology II searched the WHO COVID-19-research database and PubMed, using the search terms "PAXLOVID" and "epidemiology/RWE study" (Section 16.5.2). We excluded articles that:

- Did not report a study that evaluated PAXLOVID effectiveness.
- Did not report observational studies (e.g., articles reported clinical trials, case reports, case series).
- Did not report findings of analyses on PAXLOVID effectiveness, compared to non-PAXLOVID-treated COVID-19 patients
- Did not evaluate PAXLOVID effectiveness in an outpatient COVID-19 population

We further applied the criteria described below for selecting studies for in-depth review.

Longitudinal Data

Studies that used data source(s) that allow longitudinal capture of the key covariates across different healthcare settings:

- Diagnosis/test of COVID-19 in an ambulatory setting
- Exposure to PAXLOVID as outpatient treatment
- Vaccination status prior to COVID-19 diagnosis/PAXLOVID exposure
- Clinical outcome (hospitalization or death) after COVID-19 diagnosis/PAXLOVID exposure
- Comorbid conditions and concurrent medication use at time of COVID-19 diagnosis/PAXLOVID use

"Nonuser" Reference Group

Included "nonuser" as a reference group, since we do not have trial data to support effectiveness of PAXLOVID against an "active control" (i.e., other potential COVID-19 treatments).

Index Time Selection

Applied design feature that can account for the potential bias introduced by "index time" selection for the treated and untreated patients, given that PAXLOVID users were COVID-19 patients who remained hospitalization-free and survived from diagnosis to treatment, which can lead to bias in favor of finding PAXLOVID effectiveness.

16.5.1.2. Review Results

Our last literature search was conducted on January 30, 2023. Among the 297 English-language articles identified by our search terms, 22 were observational studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations (Section 16.5.2); we excluded:

- Three publications (Najjar-Debbiny et al. 2023; Wai et al. 2023; Yip et al. 2023), of shorter study duration, that used the same data source as another identified publication.[14]
- One publication (Xie et al. 2022),that described a study that only evaluated "post-acute sequelae of COVID-19"[15] occurring from 30 to 90 days after SARS-CoV-2 infection, due to significant design concerns:
  - The validity of code-based algorithms to capture the individual post-acute COVID-19 sequelae were not reported in the article
  - Important confounders (e.g., use of certain medications that could influence the risk of the individual clinical condition that consists of "post-acute COVID-19 sequelae") were neither reported nor accounted for in the analyses

We screened the remaining publications and further excluded 13 studies that did not meet all the key data source and design features criteria for in-depth review (Table 143).

Table 143. Screening of the Identified Observational RWE Studies on Outpatient PAXLOVID Effectiveness

	Fulfilled Key Data Source and Design Features for In-Depth Review		
Study Screened	**Longitudinal Data Source**	**Nonuser Reference Group**	**Design to Handle Bias Due to Index Time Selection**
Excluded			
(Hedvat et al. 2022)	No	Yes	No
(Dryden-Peterson et al. 2023)	No	Yes	Yes
(Ganatra et al. 2022)	No	Yes	No
(Zhou et al. 2022a)	No	Yes	Yes
(Aggarwal et al. 2023)	No	Yes	No
(Bruno et al. 2022a)	Unclear	No	N/A
(Bruno et al. 2022b)	Unclear	No	N/A
(Gentile et al. 2022)	Unclear	No	N/A
(Park et al. 2022a)	Yes	Yes	No
(Park et al. 2022b)	Yes	Yes	No
(Qian et al. 2022)	No	Yes	No
(Shah et al. 2022)	No	Yes	Unclear
(Tiseo et al. 2023)	Unclear	No	N/A

[14] The publication by Najjar-Debbiny et al. was excluded due to an overlapping Israeli data source with Arbel et al. The publications by Yip et al. and Wai et al. were based on the same territory-wide population in Hong Kong as that by Wong et al.

[15] Post-acute death or hospitalization and individual sequela including ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough.

	Fulfilled Key Data Source and Design Features for In-Depth Review		
Study Screened Included	**Longitudinal Data Source**	**Nonuser Reference Group**	**Design to Handle Bias Due to Index Time Selection**
(Arbel et al. 2022)	Yes	Yes	Yes
(Wong et al. 2022)	Yes	Yes	Yes
(Bajema et al. 2022)	Yes	Yes	Yes
(Schwartz et al. 2022)	Yes	Yes	Yes
(Lewnard et al. 2023)	Yes	Yes	Yes

Source: FDA reviewer.
Abbreviations: N/A, not applicable; RWE, real-world-evidence

Five studies were included in our in-depth review (Arbel et al. 2022; Bajema et al. 2022; Schwartz et al. 2022; Wong et al. 2022; Lewnard et al. 2023). Of note, the publications by Bajema, Schwartz, and Lewnard are non-peer-reviewed preprints.[16]

Briefly, the five reviewed studies were cohort studies involving non-hospitalized patients with positive SARS-CoV-2 RT-PCR or antigen test results during the period of Omicron-variant dominance. One study in Israel and one study in China (Hong Kong) used nation-wide or territory-wide electronic health records of hospitals and outpatient clinics. One study in Quebec, Canada used a province-wide integrated health-care data. The final two studies used electronic health records and administrative claims data; one was based on the U.S. Veterans Health Administration and the other based on an integrated healthcare system of a single U.S. state. These five studies also included broader study populations than those included in the pivotal trials—with respect to age, underlying high-risk comorbidities, and COVID-19 vaccination status.

All studies evaluated the risk of COVID-19-related hospitalization or all-cause hospitalization in PAXLOVID-treated COVID-19 patients compared to those not treated with PAXLOVID (nonusers). They also evaluated other clinical outcomes, such as mortality or in-hospital COVID-19 progression. The real-world evidence (RWE) studies in general reported PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status.

Conclusions on the Quality of the Available PAXLOVID RWE Studies

Seventeen of the twenty-two identified RWE studies reporting effectiveness of outpatient PAXLOVID use were excluded from in-depth review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources, and/or were unable to account for potential bias introduced by index time selection. The five remaining studies consistently reported that PAXLOVID use was associated with a reduced risk of worsening COVID-19 outcomes in broader populations than included in the pivotal trials, with respect to age, underlying "high-risk" comorbidities, and COVID-19 vaccination status in the Omicron era.

The information available for the reviewed observational studies was insufficient to determine their quality.

[16] The manuscripts are available as preprints; i.e., they have not been peer-reviewed. Non-peer-reviewed preprints may not be accepted for publication by a peer-reviewed journal. If they are formally published in a peer-reviewed journal, there may be revisions of the methods or analyses to address the editor's or reviewers' comments.

Details on the Assessment of the Eligible PAXLOVID RWE Studies That Informed the Conclusions

Compared to the studies excluded from in-depth review, the five reviewed RWE studies used more appropriate data sources, study design, or analytical approaches to account for the potential bias introduced by inappropriate handling of index time selection.

However, unlike Applicant-sponsored efficacy trials that provide more information to assess study quality, none of the reviewed RWE studies published their protocol and analytical plan prior to the final study report. In at least one study, Lewnard et al., the analyses and results differed notably between two version of the preprints (Lewnard et al. 2023). So, it was difficult to track whether these studies were conducted according to a prespecified protocol and analytical plan. Additionally, patient-level data on the observational studies were unavailable to verify the correct implementation of study design and statistical methods, which is a standard review process for trial data that are used to support treatment efficacy.

Despite insufficient information on studies due to what is reported in the public domain, we still identified methodological or analytical issues in the reviewed studies. Some of these issues had reasonably predictable impact on the study findings, while there were other review issues for which we would need more information than was provided to determine the potential impact on the study results. These issues are summarized below.

Review Issues With a Reasonably Predictable Impact on Study Findings

Residual Confounding by COVID-19 Severity (All Studies)

Three of the reviewed studies did not capture or adjust for baseline COVID-19 severity (Arbel et al. 2022; Schwartz et al. 2022; Wong et al. 2022). The studies by Bajema and Lewnard accounted for the presence of COVID-19 symptoms at baseline; however, the validity of the operational definitions for COVID-19 symptoms was not reported (Bajema et al. 2022; Lewnard et al. 2023). Residual confounding due to COVID-19 severity would likely to underestimate of PAXLOVID effectiveness, given that PAXLOVID was more likely to be given to symptomatic patients or patients with severe symptoms.

Residual Confounding by High-Risk Comorbidities (Arbel and Wong Studies)

Although the Arbel study captured information on medical conditions that increase a patient's risk for COVID-19 progression (high-risk comorbidities), not all were adjusted for in the analyses (Arbel et al. 2022). The Wong study matched the treated and non-treated patients on a summary comorbidity risk score (i.e., Charlson Comorbidity Index), which did not guarantee the component medical conditions of the risk score would be balanced between treatment groups (Wong et al. 2022). Furthermore, the component medical conditions of the Charlson Comorbidity Index were not an exact match to the high-risk comorbidities for worse COVID-19 progression. For example, the Charlson Comorbidity Index does not account for all immunosuppressive diseases (e.g., bone marrow or organ transplantation), prolonged use of immune-weakening medications, chronic lung diseases (except for chronic obstructive pulmonary disease), neurodevelopmental disorders, sickle cell disease. Lastly, the Wong study

did not report distribution of high-risk comorbidities for COVID-19 progression to inform if these important confounders were balanced between treatment groups.

Residual confounding due to unbalanced high-risk comorbidities would likely underestimate of PAXLOVID effectiveness, given that PAXLOVID treatment for COVID-19 patients with high-risk comorbidities was likely prioritized.

Outcome Selection (Bajema and Lewnard Studies)

Studies by Bajema and Lewnard used "all-cause hospitalization or death" as the primary outcome, which included events that are unrelated to PAXLOVID effect (i.e., hospitalization or death due to causes other than COVID-19) (Bajema et al. 2022; Lewnard et al. 2023). If the proportion of outcome events unrelated to COVID-19 is nondifferential between treated and nontreated groups, it would bias findings toward null (underestimate of PAXLOVID effectiveness). The proportion of events unrelated to COVID-19 can be higher among PAXLOVID users, given that administration of PAXLOVID is prioritized to patients with comorbidities that may lead to a higher risk of hospitalization or death due to non-COVID-19 causes, which will also lead to underestimate of PAXLOVID effectiveness.

Study Power to Evaluate PAXLOVID Effectiveness in Subgroups (All Studies)

Only one reviewed study reported a priori power analyses (Bajema et al. 2022). All the reviewed studies were not powered to formally test treatment effect modification by patient characteristics, or to evaluate PAXLOVID effectiveness in any patient subgroup. Some studies suggested that PAXLOVID effectiveness may differ by age, for example, Arbel concluded that "no evidence of benefit was found in patients younger than 65 years of age" (Arbel et al. 2022). The study findings did not support a statistically significant reduction in COVID-19 hospitalization risk (hazard ratio = 0.74, 95% CI = 0.35 to 1.58) or death (hazard ratio = 1.32, 95% CI = 0.16 to 10.75) associated with PAXLOVID use among a younger population (40 to 65 years of age). However, it is likely that the study did not have sufficient power to evaluate PAXLOVID effectiveness in the younger population, evidenced by the wide 95% CIs of the effect estimates.

Review Issues That Require More Information to Evaluate the Impact on Study Results

Unvalidated Outcome Measures

COVID-19-Related Hospitalization (Arbel, Wong, and Schwartz Studies)

Three reviewed studies included "hospitalization due to COVID-19" as the endpoint, or part of the endpoints (Arbel et al. 2022; Schwartz et al. 2022; Wong et al. 2022). However, none of the studies provided data to support the validity of the measure for "COVID-related hospitalization." Without a better understanding of how information on COVID-19 related hospitalization was recorded or derived, it is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Post-COVID-19 Conditions (Bajema Study)

The Bajema study also evaluated PAXLOVID's effectiveness on multiple potential post-COVID-19 conditions (Bajema et al. 2022);[17] however, they did not provide data to support the International Classification of Diseases, 10th Edition diagnosis codes that were used to capture these conditions (WHO 2019). It is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Residual Confounding by Other Potential Confounders

Information on the frequencies and the distribution of the potential confounders (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Detailed Information on COVID-19 Vaccination (Arbel, Wong, and Lewnard Studies)

Total dose, timing of last dose, type or manufacturer of the COVID-19 vaccine could impact PAXLOVID effectiveness for COVID-19 outcomes. Not all reviewed studies captured or accounted for detailed information on COVID-19 vaccination in their analyses. The Arbel and Wong studies only reported and accounted for vaccination status as dichotomous variables ("presence of prior immunity or not" in Arbel study, "fully vaccinated or not" in the Wong study) (Arbel et al. 2022; Wong et al. 2022). The Lewnard study only adjusted for the number of total vaccine doses received in their analyses (Lewnard et al. 2023).

Other Outpatient COVID-19 Medication Use at Baseline (Lewnard Study)

Prior or concurrent use of other outpatient medications for COVID-19 at baseline can be a potential confounder as they can influence COVID-19-related clinical outcomes. The Lewnard study did not exclude patients who used other COVID-19 medications at baseline, while several treatment options were available in the United States during the timeframe of the study (Lewnard et al. 2023). The study also did not report the use of the other outpatient COVID-19 treatment at baseline, nor adjusted for baseline use of these medications in their analyses.

Other Medications Use (Bajema Study)

The Bajema study included analyses of PAXLOVID effectiveness on risk of long-term outcomes (i.e., hospital admission, nursing skilled nursing home facility admission, all-cause death, or post-COVID-19 conditions) that occurred 31 to 180 days after diagnosis (Bajema et al. 2022).

[17] Post-COVID-19 conditions in the Bajema study comprise: acute coronary syndrome, cardiac dysrhythmias, cardiovascular disease, chest pain, heart failure and cardiomyopathy, hypertension, myocarditis, respiratory symptoms (shortness of breath/dyspnea, any respiratory distress/failure, any bronchitis, hypoxemia, bronchiectasis, any non-COVID-19 pneumonia including influenza, cough, wheezing, sneezing, nasal congestion/sinusitis, sore throat, pharyngitis, laryngitis, tonsillitis), asthma, COPD and emphysema, obstructive sleep apnea or obesity hypoventilation, renal conditions (acute kidney injury, chronic kidney disease, dialysis), venous thromboembolism, pulmonary embolism, abdominal pain, esophageal disorders, gastrointestinal disorders, cerebrovascular disease, dementia, smell and taste disturbance, headache, sleeping disorders, other neurologic conditions (peripheral nerve disorders [i.e., neuropathy, Guillain-Barre syndrome], epilepsy, multiple sclerosis, complex regional pain syndrome, Parkinson disease), depression, other mood disorders (bipolar, schizophrenia, psychosis), anxiety, PTSD, substance-related disorder, musculoskeletal conditions (any myositis, muscle wasting and atrophy, contracture of muscle, myalgias), diabetes, disorders of lipid metabolism, obesity, malaise and fatigue

PAXLOVID was prioritized for patients with COVID-19 and certain comorbidities that are also components of the "post-COVID conditions;" for example, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, diabetes, obesity. The use of other medications, especially those that are indicated for the components of the post-COVID-19 conditions, are important confounders that were not reported, nor accounted for in the study.

Handling of Post-Index Time COVID-19 Treatment

Information on the frequencies and the distribution of post-index time COVID-19 treatment changes (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Other Outpatient COVID-19 Medication Use (All Studies)

In the analyses of PAXLOVID's effectiveness on hospitalization, use of other outpatient COVID-19 medications during follow-up could be on the causal pathway between PAXLOVID use and COVID-19 outcome- the need to use another treatment can be an early indication that PAXLOVID did not work well in preventing disease progression. Use of other COVID-19 treatments also have an impact on COVID-19 outcome, independently from PAXLOVID's effectiveness.

Use of other outpatient COVID-19 medications was a censor criterion in the Wong study, but not in the Lewnard or Bajema studies, while the Arbel and Schwartz studies did not clearly state how they handled patients who initiated another outpatient COVID-19 treatment during follow-up (Arbel et al. 2022; Bajema et al. 2022; Schwartz et al. 2022; Wong et al. 2022; Lewnard et al. 2023). If the use of other outpatient COVID-19 medication is uncommon, these different approaches would likely all be acceptable; however, none of the three reviewed studies reported the extent of other COVID-19 medications used during follow-up.

Inpatient Medical Management (Arbel, Wong, Bajema, and Lewnard Studies)

Four of the reviewed studies (Arbel, Wong, Bajema, and Lewnard) also evaluated outpatient PAXLOVID's impact on in-patient outcomes, such as in-hospital disease progression, invasive mechanical ventilation use, intensive care unit admission and death, or post-acute COVID-19 symptoms (Arbel et al. 2022; Bajema et al. 2022; Wong et al. 2022; Lewnard et al. 2023). In these analyses, the medical treatment that patients received during hospitalization, such as inpatient COVID-19 treatment, could be on the causal pathway. None of these studies reported information on inpatient medical management during follow-up, nor accounted for its impact in the analyses.

Concern on Statistical Methods

Ambiguous Statistical Methods and Results (Lewnard Study)

The details of the analyses and the results are not clear. Without knowledge of the details, some of the results are difficult to review and interpret. The definition of the discordant pairs in the results tables (Table 2 and Table 3) is not clear and the summaries of the discordant pairs do not seem to align with the effectiveness estimates (Lewnard et al. 2023). It is also unclear whether immortal time in treated subjects is handled properly when determining discordant pairs. In

addition, about 42% of eligible PAXLOVID-treated patients were not included in the analyses, calling into question the generalizability of the results.

Handling of Immortal Time Bias (Schwartz and Wong Studies)

The Schwartz study assigned random index dates to the unexposed group based on the time-to-dispense distribution from the exposed group (Schwartz et al. 2022). This approach did not consider factors that may impact the dispensing time for each subject (e.g., the presence of symptoms) and may not fully fix the immortal time bias problem.

The primary analyses of the Wong study set the index time at COVID-19 symptom onset or diagnosis, which introduced immortal time in the PAXLOVID-treated group and could overestimate PAXLOVID effectiveness (Wong et al. 2022). The investigators conducted post hoc sensitivity analyses that treated exposure status as a "time-varying" variable to account for immortal time bias. The findings of this sensitivity analysis that accounted for immortal time bias consistently support PAXLOVID effectiveness as the primary analyses in the overall study population. It is unclear if the conclusion would be the same for the subgroup analyses stratified by vaccination status, as the author did not report the findings of the sensitivity analyses by patient subgroup.

Handling of Missing Data (All Studies)

All the studies except for the Lewnard study did not report the degree of missing data for important baseline covariates (Lewnard et al. 2023). Most of the studies did not specify a method of handling missing data other than excluding subjects with missing covariates.

16.5.2. RWE Literature Search Process (Steps and Numbers of Articles Remaining)

English language articles with "Paxlovid OR nirmatrelvir" AND keywords of "epidemiology or RWE study," *excluding* animal, cellular, pharmacokinetic/pharmacodynamics, identified 297 articles (*search terms are required in Title, Abstract, or Subject*).

- Restrict to studies evaluating PAXLOVID effectiveness 44
- Exclude duplicate publications 26
- Exclude studies involving hospitalized subjects with COVID-19 22

16.5.2.1. RWE Literature Search Terms

Key Words for Epidemiology or RWE Studies

epidemiology OR observational OR non-randomized OR cohort OR sample OR adjustment OR "propensity score" OR "inverse probability weighting" OR "integrated health care system" OR multivariate OR multivariable OR population-based OR case-control OR database OR bayesian OR abstracted OR "convenience sample" OR "electronic health record" OR "systematic review" OR cohort OR case-control OR database OR datalink OR "claims data" OR "drug utilization" OR "electronic health records" OR "electronic medical records" OR biobank OR "pooled analysis" OR crossover OR registry OR registries OR meta-analysis OR retrospective OR

Reference ID: 5179402

prospective OR "cross sectional" OR cross-sectional OR "prevalence study" OR "longitudinal study" OR "before-after study" OR "administrative database" OR "insurance claim" OR matched-cohort OR population-based OR "insurance database" OR "claims database" OR "pharmaceutical claims" OR "case control" OR "meta analysis" OR self-controlled OR "self controlled" OR comparative OR emr OR prevalence OR incidence OR rate OR "administrative claim" OR “Real-World” OR “Real World” OR “RWE”.

Key Words for Animal, Cellular, and Pharmacokinetic/Pharmacodynamics Studies (for Exclusion)

animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosophila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR atlantic cod OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR

llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR polymorphism OR plant OR pharmacokinetics OR pharmacokinetic OR pharmacodynamic OR pharmacodynamics.

17. Clinical Safety

17.1. Adverse Event Definitions

AEs were defined in the protocol as: “An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.”

Treatment-emergent adverse events (TEAEs) were defined in the Applicant’s analysis plan, and for the purpose of this review, as: “Any AE that occurred on or after the medication start date and time.”

Adverse drug reactions were defined for the purpose of this review as: “Any TEAE that was considered by the investigator to be related to the study drug with reasonable possibility.”

“Reasonable possibility” of a relationship was defined in the protocol to convey that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Serious adverse events (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

- Results in death.
- Is life threatening. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- If suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

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17.2. Deaths, EPIC-HR and EPIC-SR

Table 144 and Table 145 describe deaths in EPIC-HR and EPIC-SR.

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Table 144. Deaths[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Any AE leading to death	0	13 (1.2)	-1.2 (-1.9, -0.6)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	14 (0.9)	-0.9 (-1.3, -0.4)*
Acute respiratory failure	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pneumonitis	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
COVID-19	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)
COVID-19 pneumonia	0	8 (0.8)	-0.8 (-1.3, -0.2)*	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	9 (0.6)	-0.6 (-0.9, -0.2)*

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (incl. those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (incl. those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Difference is shown between PAXLOVID vs placebo
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; N, number of patients in treatment arm; n, number of patients with adverse event

Table 145. Listing of All Individual Patient Deaths[1], Safety Population, EPIC-HR and EPIC-SR[2]

					Dosing Duration	Study Day	Cause of Death	
Study Arm	Patient ID	Age	Sex	Dosage	(Days)	of Death	Preferred Term	Verbatim Term
EPIC-HR Placebo	(b) (6)	75	M	NA	3	9	COVID-19	COVID-19 worsening
EPIC-HR Placebo		73	M	NA	5	9	COVID-19 pneumonia	Respiratory failure caused by COVID-19 pneumonia
EPIC-HR Placebo		72	M	NA	3	32	Pneumonitis	Progression of the lung inflammation
EPIC-HR Placebo		52	M	NA	2	11	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		68	F	NA	5	9	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		72	F	NA	4	13	COVID-19 pneumonia	COVID-19 bilateral pneumonia
EPIC-HR Placebo		67	F	NA	2	4	COVID-19 pneumonia	COVID 19 bilateral pneumonia
EPIC-HR Placebo		70	M	NA	5	11	COVID-19 pneumonia	Death due to COVID-19 pneumonia
EPIC-HR Placebo		75	M	NA	5	25	COVID-19 pneumonia	Bilateral COVID-19 pneumonia
EPIC-HR Placebo		84	F	NA	2	9	COVID-19 pneumonia	COVID-19 pneumonia
EPIC-HR Placebo		54	M	NA	5	27	COVID-19	COVID-19 complications
EPIC-HR Placebo		61	M	NA	5	12	COVID-19	COVID-19
EPIC-HR Placebo		64	M	NA	4	12	Acute respiratory failure	Acute respiratory failure
EPIC-SR Placebo		67	M	NA	5	6	COVID-19 pneumonia	COVID-19 pneumonia

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (incl. those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (incl. those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; F, female; ID, identifier; M, male; NA, not applicable

17.3. Safety Results, Vaccinated Participants With at Least One Risk Factor for Progression to Severe Disease, EPIC-SR

Table 146 provides a summary of TEAEs reported through Day 34 in subjects who were vaccinated with at least one risk factor for progression to severe disease in EPIC-SR. The frequencies of severe (Grade 3) or higher TEAEs were similar in the PAXLOVID group when compared to the placebo group in these subjects. There were no SAEs or deaths in the PAXLOVID group, and five (1.6%) subjects had an AE leading to permanent discontinuation of study drug. The frequency of any AE was similar between the PAXLOVID and placebo groups.

Table 146. Overview of Adverse Events[1], Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Event Category	PAXLOVID N=317 n (%)	Placebo N=314 n (%)	Risk Difference (%) (95% CI)[3]
SAE	5 (1.6)	8 (2.5)	-1.0 (-3.2, 1.2)
SAEs with fatal outcome	0	1 (0.3)	-0.3 (-0.9, 0.3)
Life-threatening SAEs	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
AE leading to permanent discontinuation of study drug	5 (1.6)	4 (1.3)	0.3 (-1.5, 2.2)
AE leading to dose modification of study drug	0	1 (0.3)	-0.3 (-0.9, 0.3)
AE leading to interruption of study drug	0	1 (0.3)	-0.3 (-0.9, 0.3)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE[4]	80 (25.2)	84 (26.8)	-1.5 (-8.4, 5.3)
Severe and worse	12 (3.8)	16 (5.1)	-1.3 (-4.5, 1.9)
Moderate	22 (6.9)	20 (6.4)	0.6 (-3.3, 4.5)
Mild	46 (14.5)	48 (15.3)	-0.8 (-6.3, 4.8)

Source: adae.xpt; Software: R.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Difference is shown between PAXLOVID and placebo.
4. Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

When comparing the vaccinated subjects with at least one risk factor for progression to severe disease in EPIC-SR, the incidence of overall TEAEs were similar between the PAXLOVID group when compared to the placebo group. Table 147 summarizes the AEs occurring in at least 0.5% of subjects in any group.

Table 147. Patients With Common Adverse Events[1] Occurring at ≥0.5% Frequency, Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Preferred Term	PAXLOVID N=317 n (%)	Placebo N=314 n (%)	Risk Difference (%) (95% CI)[3]
Any AE	80 (25.2)	84 (26.8)	-1.5 (-8.4, 5.3)
Dysgeusia	16 (5.0)	1 (0.3)	4.7 (2.2, 7.2)*
Headache	6 (1.9)	2 (0.6)	1.3 (-0.5, 3.0)
Aspartate aminotransferase increased	4 (1.3)	1 (0.3)	0.9 (-0.4, 2.3)
Blood lactate dehydrogenase increased	2 (0.6)	0	0.6 (-0.2, 1.5)
Hypothyroidism	2 (0.6)	0	0.6 (-0.2, 1.5)
Prothrombin time prolonged	2 (0.6)	0	0.6 (-0.2, 1.5)
Pruritus	2 (0.6)	0	0.6 (-0.2, 1.5)
Renal failure	2 (0.6)	0	0.6 (-0.2, 1.5)
C-reactive protein increased	3 (0.9)	1 (0.3)	0.6 (-0.6, 1.9)
Dyspepsia	4 (1.3)	2 (0.6)	0.6 (-0.9, 2.1)
Creatinine renal clearance decreased	5 (1.6)	3 (1.0)	0.6 (-1.1, 2.4)
Alanine aminotransferase increased	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Dehydration	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Hepatic enzyme increased	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Type 2 diabetes mellitus	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)
Hyperkalemia	2 (0.6)	2 (0.6)	-0.0 (-1.2, 1.2)
Hypertension	2 (0.6)	2 (0.6)	-0.0 (-1.2, 1.2)
Nausea	12 (3.8)	12 (3.8)	-0.0 (-3.0, 2.9)
Diarrhea	14 (4.4)	14 (4.5)	-0.0 (-3.3, 3.2)
Asthenia	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Back pain	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Blood thyroid stimulating hormone increased	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.8)
Dyspnea	2 (0.6)	3 (1.0)	-0.3 (-1.7, 1.1)
Alopecia	0	2 (0.6)	-0.6 (-1.5, 0.2)
Bronchospasm	0	2 (0.6)	-0.6 (-1.5, 0.2)
Flatulence	0	2 (0.6)	-0.6 (-1.5, 0.2)
Migraine	0	2 (0.6)	-0.6 (-1.5, 0.2)
Musculoskeletal pain	0	2 (0.6)	-0.6 (-1.5, 0.2)
Productive cough	0	2 (0.6)	-0.6 (-1.5, 0.2)
Rhinitis allergic	0	2 (0.6)	-0.6 (-1.5, 0.2)
Blood creatine phosphokinase increased	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Fibrin D dimer increased	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Tachycardia	1 (0.3)	3 (1.0)	-0.6 (-1.9, 0.6)
Activated partial thromboplastin time prolonged	2 (0.6)	4 (1.3)	-0.6 (-2.2, 0.9)
Vomiting	5 (1.6)	7 (2.2)	-0.7 (-2.8, 1.5)
Abdominal pain upper	0	3 (1.0)	-1.0 (-2.0, 0.1)
Pneumonia	0	4 (1.3)	-1.3 (-2.5, -0.0)*
Dizziness	1 (0.3)	5 (1.6)	-1.3 (-2.8, 0.2)
COVID-19 pneumonia	2 (0.6)	8 (2.5)	-1.9 (-3.9, 0.0)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Coded as MedDRA preferred terms.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs. placebo
Abbreviations: CI, confidence interval; COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

The incidence of TEAEs among PAXLOVID recipients was similar in the seropositive (21.5%, 197/918) and seronegative subgroups (23.9%, 152/637). The most common adverse events in PAXLOVID recipients were dysgeusia (4.7% in the seronegative subgroup and 5.1% in the seropositive subgroup) and diarrhea (3.3% in the seronegative subgroup and 3.5% in the seropositive subgroup)[18].

Additionally, the incidence of TEAE in subjects in EPIC-SR who were unvaccinated was similar between the PAXLOVID group (21.8%, 272/1248) and the placebo group (23.5%, 296/1259). The most common adverse events in recipients of PAXLOVID in the unvaccinated subgroup were dysgeusia (5.0%) and diarrhea (3.0%)[19].

17.4. Adverse Event Assessment, EPIC-HR and EPIC-SR

Overviews of adverse events in EPIC-HR and EPIC-SR were provided in Sections 7.6.1.3, 7.6.1.4, and 7.6.1.5 Assessment of SAEs using FDA medical queries (FMQs) (Table 148), AEs leading to treatment discontinuation (Table 149), and subjects with adverse events (Table 150 and Table 151) were similar to the respective assessments using preferred terms.

[18] Source: Applicant's Table 84d.3.1.2.2.13i, Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities), by Baseline Serology Status

[19] Source: Applicant's Table 84d.3.1.2.2.10i, Treatment-Emergent Adverse Events by System Organ Class and Preferred Term [All Causalities], by Vaccination Status

Table 148. Patients With Serious Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ[4] (Narrow)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)									
Anemia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Thrombosis	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Thrombosis venous	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Cardiac disorders (SOC)									
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Systemic hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hepatobiliary disorders (SOC)									
Hepatic injury	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Infections and infestations (SOC)									
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Bacterial infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Pneumonia	1 (0.1)	12 (1.1)	-1.0 (-1.7, -0.4)*	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	3 (0.2)	14 (0.9)	-0.7 (-1.2, -0.2)*
Viral infection	9 (0.9)	43 (4.1)	-3.2 (-4.5, -1.9)*	3 (0.6)	9 (1.7)	-1.1 (-2.4, 0.1)	12 (0.8)	52 (3.3)	-2.5 (-3.5, -1.6)*
Musculoskeletal and connective tissue disorders (SOC)									
Fracture	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Nervous system disorders (SOC)									
Stroke TIA	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Dyspnea	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Respiratory failure	1 (0.1)	6 (0.6)	-0.5 (-1.0, 0.0)	0	0	0 (0, 0)	1 (0.06)	6 (0.4)	-0.3 (-0.6, 0.0)
Pneumonitis	0	7 (0.7)	-0.7 (-1.2, -0.2)*	0	0	0 (0, 0)	0	7 (0.4)	-0.4 (-0.8, -0.1)*

System Organ Class FMQ[4] (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Vascular disorders (SOC)									
Hemorrhage	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)

Source: adae.xpt; Software: R
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID and placebo
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 149. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

System Organ Class[4] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)									
Leukopenia	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Anemia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Cardiac disorders (SOC)									
Palpitations	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Systemic hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Endocrine disorders (SOC)									
Hyperglycemia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Gastrointestinal disorders (SOC)									
Diarrhea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
Abdominal pain	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Nausea	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	1 (0.2)	0	0.2 (-0.2, 0.5)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
Vomiting	4 (0.4)	2 (0.2)	0.2 (-0.3, 0.7)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)

System Organ Class[4] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
General disorders and administration site conditions (SOC)									
Dizziness	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Fatigue	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Peripheral edema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hepatobiliary disorders (SOC)									
Hepatic injury	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Infections and infestations (SOC)									
Pneumonia	0	3 (0.3)	-0.3 (-0.6, 0.0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Viral infection	2 (0.2)	15 (1.4)	-1.2 (-2.0, -0.5)*	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	17 (1.1)	-0.9 (-1.5, -0.4)*
Musculoskeletal and connective tissue disorders (SOC)									
Myalgia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Nervous system disorders (SOC)									
Dysgeusia	2 (0.2)	0	0.2 (-0.1, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	4 (0.3)	0	0.3 (0.0, 0.5)*
Psychiatric disorders (SOC)									
Insomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Reproductive system and breast disorders (SOC)									
Abnormal uterine bleeding	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Dyspnea	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Cough	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Respiratory failure	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Pneumonitis	0	4 (0.4)	-0.4 (-0.8, -0.0)*	0	0	0 (0, 0)	0	4 (0.3)	-0.3 (-0.5, -0.0)*

System Organ Class[4] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Skin and subcutaneous tissue disorders (SOC)									
Rash	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Vascular disorders (SOC)									
Hemorrhage	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2]Duration of treatment is 5 days.
[3] Difference is shown between PAXLOVID vs placebo.
[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 150. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-HR and EPIC-SR[2]

System Organ Class[3] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[4]
Blood and lymphatic system disorders (SOC)									
Leukopenia	4 (0.4)	5 (0.5)	-0.1 (-0.7, 0.5)	0	0	0 (0, 0)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)
Anemia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Thrombosis	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Thrombocytopenia	1 (0.1)	4 (0.4)	-0.3 (-0.7, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Thrombosis venous	0	3 (0.3)	-0.3 (-0.6, 0.0)	0	0	0 (0, 0)	0	3 (0.2)	-0.2 (-0.4, 0.0)
Cardiac disorders (SOC)									
Systemic hypertension	8 (0.8)	3 (0.3)	0.5 (-0.1, 1.1)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	10 (0.6)	7 (0.4)	0.2 (-0.3, 0.7)
Heart failure	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Palpitations	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Tachycardia	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Arrhythmia	0	3 (0.3)	-0.3 (-0.6, 0.0)	2 (0.4)	5 (0.9)	-0.6 (-1.5, 0.4)	2 (0.1)	8 (0.5)	-0.4 (-0.8, 0.0)

System Organ Class[3] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[4]
Ear and labyrinth disorders (SOC)									
Vertigo	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
Endocrine disorders (SOC)									
Hypoglycemia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hyperglycemia	8 (0.8)	16 (1.5)	-0.7 (-1.7, 0.2)	5 (0.9)	3 (0.6)	0.4 (-0.7, 1.4)	13 (0.8)	19 (1.2)	-0.4 (-1.1, 0.3)
Gastrointestinal disorders (SOC)									
Diarrhea	31 (3.0)	16 (1.5)	1.5 (0.2, 2.7)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	53 (3.4)	32 (2.0)	1.3 (0.2, 2.5)*
Vomiting	12 (1.2)	9 (0.9)	0.3 (-0.6, 1.2)	10 (1.9)	11 (2.1)	-0.2 (-1.9, 1.4)	22 (1.4)	20 (1.3)	0.1 (-0.7, 0.9)
Dyspepsia	7 (0.7)	6 (0.6)	0.1 (-0.6, 0.8)	5 (0.9)	5 (0.9)	-0.0 (-1.2, 1.1)	12 (0.8)	11 (0.7)	0.1 (-0.5, 0.7)
Dry mouth	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Abdominal pain	6 (0.6)	5 (0.5)	0.1 (-0.5, 0.7)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Constipation	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Nausea	15 (1.4)	19 (1.8)	-0.4 (-1.4, 0.7)	17 (3.1)	16 (3.0)	0.1 (-2.0, 2.2)	32 (2.0)	35 (2.2)	-0.2 (-1.2, 0.8)
General disorders and administration site conditions (SOC)									
Pyrexia	8 (0.8)	7 (0.7)	0.1 (-0.6, 0.8)	3 (0.6)	1 (0.2)	0.4 (-0.4, 1.1)	11 (0.7)	8 (0.5)	0.2 (-0.3, 0.7)
Volume depletion	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	4 (0.3)	2 (0.1)	0.1 (-0.2, 0.4)
Local administration reaction	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Fall	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Peripheral edema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Dizziness	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Fatigue	5 (0.5)	8 (0.8)	-0.3 (-1.0, 0.4)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	7 (0.4)	11 (0.7)	-0.3 (-0.8, 0.3)
Hepatobiliary disorders (SOC)									
Hepatic injury	20 (1.9)	31 (2.9)	-1.0 (-2.3, 0.3)	13 (2.4)	10 (1.9)	0.5 (-1.2, 2.3)	33 (2.1)	41 (2.6)	-0.5 (-1.6, 0.6)
Immune system disorders (SOC)									
Hypersensitivity	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Infections and infestations (SOC)									
Opportunistic infection	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Fungal infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Bacterial infection	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	6 (0.4)	7 (0.4)	-0.1 (-0.5, 0.4)
Nasopharyngitis	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	6 (1.1)	-1.0 (-1.9, 0.0)	3 (0.2)	7 (0.4)	-0.3 (-0.6, 0.1)
Pneumonia	2 (0.2)	17 (1.6)	-1.4 (-2.2, -0.6)*	3 (0.6)	5 (0.9)	-0.4 (-1.4, 0.6)	5 (0.3)	22 (1.4)	-1.1 (-1.7, -0.4)*
Viral infection	15 (1.4)	59 (5.6)	-4.2 (-5.7, -2.6)*	4 (0.7)	12 (2.3)	-1.5 (-3.0, -0.1)*	19 (1.2)	71 (4.5)	-3.3 (-4.4, -2.1)*

System Organ Class[3] FMQ (Narrow)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[4]
Metabolism and nutrition disorders (SOC)									
Lipid disorder	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)									
Myalgia	7 (0.7)	1 (0.09)	0.6 (0.0, 1.1)*	0	0	0 (0, 0)	7 (0.4)	1 (0.06)	0.4 (0.0, 0.7)*
Arthralgia	3 (0.3)	1 (0.09)	0.2 (-0.2, 0.6)	0	0	0 (0, 0)	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.4)
Gout	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Back pain	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	3 (0.2)	4 (0.3)	-0.1 (-0.4, 0.3)
Rhabdomyolysis	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fracture	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Nervous system disorders (SOC)									
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	30 (5.6)	2 (0.4)	5.2 (3.2, 7.2)*	78 (4.9)	3 (0.2)	4.8 (3.7, 5.8)*
Stroke TIA	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Syncope	0	1 (0.09)	-0.1 (-0.3, 0.1)	2 (0.4)	0	0.4 (-0.1, 0.9)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Confusional state	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Somnolence	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Tremor	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	8 (1.5)	-0.4 (-1.8, 1.0)	18 (1.1)	21 (1.3)	-0.2 (-1.0, 0.6)
Psychiatric disorders (SOC)									
Insomnia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Irritability	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Anxiety	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Arthritis	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	2 (0.1)	0.0 (-0.2, 0.2)
Depression	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Renal and urinary disorders (SOC)									
Renal and urinary tract infection	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Reproductive system and breast disorders (SOC)									
Excessive menstrual bleeding	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abnormal uterine bleeding	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	0	0 (0, 0)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class[3] FMQ (Narrow)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[4]
Respiratory, thoracic, and mediastinal disorders (SOC)									
Cough	8 (0.8)	6 (0.6)	0.2 (-0.5, 0.9)	0	3 (0.6)	-0.6 (-1.2, 0.1)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	3 (0.6)	3 (0.6)	-0.0 (-0.9, 0.9)	10 (0.6)	12 (0.8)	-0.1 (-0.7, 0.5)
Bronchospasm	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Respiratory failure	2 (0.2)	8 (0.8)	-0.6 (-1.2, 0.0)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	8 (0.5)	-0.3 (-0.7, 0.1)
Pneumonitis	1 (0.1)	8 (0.8)	-0.7 (-1.2, -0.1)*	0	0	0 (0, 0)	1 (0.06)	8 (0.5)	-0.4 (-0.8, -0.1)*
Skin and subcutaneous tissue disorders (SOC)									
Pruritus	1 (0.1)	0	0.1 (-0.1, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	0	0.2 (-0.0, 0.4)
Rash	5 (0.5)	5 (0.5)	0.0 (-0.6, 0.6)	0	0	0 (0, 0)	5 (0.3)	5 (0.3)	0.0 (-0.4, 0.4)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Urticaria	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Erythema	0	4 (0.4)	-0.4 (-0.8, -0.0)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Vascular disorders (SOC)									
Hemorrhage	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Hypotension	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	3 (0.6)	0	0.6 (-0.1, 1.2)	4 (0.3)	5 (0.3)	-0.1 (-0.4, 0.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 151. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Broad), Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ (Broad)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)									
Thrombosis arterial	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Anemia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	2 (0.4)	-0.4 (-0.9, 0.1)	2 (0.1)	4 (0.3)	-0.1 (-0.4, 0.2)
Thrombocytopenia	1 (0.1)	4 (0.4)	-0.3 (-0.7, 0.1)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Thrombosis	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	0	0	0 (0, 0)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Thrombosis venous	0	5 (0.5)	-0.5 (-0.9, -0.1)*	0	0	0 (0, 0)	0	5 (0.3)	-0.3 (-0.6, -0.0)*
Leukopenia	4 (0.4)	10 (0.9)	-0.6 (-1.3, 0.1)	0	0	0 (0, 0)	4 (0.3)	10 (0.6)	-0.4 (-0.8, 0.1)
Cardiac disorders (SOC)									
Systemic hypertension	8 (0.8)	3 (0.3)	0.5 (-0.1, 1.1)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	10 (0.6)	7 (0.4)	0.2 (-0.3, 0.7)
Palpitations	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Cardiac conduction disturbance	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Myocardial infarction	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Myocardial ischemia	0	0	0 (0, 0)	0	2 (0.4)	-0.4 (-0.9, 0.1)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Tachycardia	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Heart failure	7 (0.7)	10 (0.9)	-0.3 (-1.0, 0.5)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	9 (0.6)	14 (0.9)	-0.3 (-0.9, 0.3)
Acute coronary syndrome	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	5 (0.9)	-0.2 (-1.3, 0.9)	5 (0.3)	10 (0.6)	-0.3 (-0.8, 0.2)
Arrhythmia	5 (0.5)	11 (1.0)	-0.6 (-1.3, 0.2)	9 (1.7)	12 (2.3)	-0.6 (-2.3, 1.1)	14 (0.9)	23 (1.5)	-0.6 (-1.3, 0.2)
Ear and labyrinth disorders (SOC)									
Vertigo	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Endocrine disorders (SOC)									
Hypoglycemia	3 (0.3)	1 (0.09)	0.2 (-0.2, 0.6)	0	1 (0.2)	-0.2 (-0.6, 0.2)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Diabetic ketoacidosis	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Hyperglycemia	9 (0.9)	17 (1.6)	-0.7 (-1.7, 0.2)	5 (0.9)	3 (0.6)	0.4 (-0.7, 1.4)	14 (0.9)	20 (1.3)	-0.4 (-1.1, 0.3)
Eye disorders (SOC)									
Glaucoma	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Gastrointestinal disorders (SOC)									
Diarrhea	32 (3.1)	17 (1.6)	1.5 (0.2, 2.8)*	22 (4.1)	16 (3.0)	1.0 (-1.2, 3.3)	54 (3.4)	33 (2.1)	1.3 (0.2, 2.5)*
Dyspepsia	14 (1.3)	9 (0.9)	0.5 (-0.4, 1.4)	9 (1.7)	7 (1.3)	0.3 (-1.1, 1.8)	23 (1.5)	16 (1.0)	0.4 (-0.3, 1.2)
Dry mouth	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Abdominal pain	6 (0.6)	5 (0.5)	0.1 (-0.5, 0.7)	2 (0.4)	4 (0.8)	-0.4 (-1.3, 0.5)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Constipation	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Nausea	21 (2.0)	25 (2.4)	-0.4 (-1.6, 0.9)	23 (4.3)	23 (4.4)	-0.1 (-2.5, 2.3)	44 (2.8)	48 (3.0)	-0.2 (-1.4, 0.9)
Vomiting	21 (2.0)	26 (2.5)	-0.4 (-1.7, 0.8)	23 (4.3)	23 (4.4)	-0.1 (-2.5, 2.3)	44 (2.8)	49 (3.1)	-0.3 (-1.5, 0.9)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ (Broad)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)
General disorders and administration site conditions (SOC)									
Pyrexia	9 (0.9)	7 (0.7)	0.2 (-0.5, 0.9)	4 (0.7)	1 (0.2)	0.6 (-0.3, 1.4)	13 (0.8)	8 (0.5)	0.3 (-0.2, 0.9)
Volume depletion	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Local administration reaction	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Peripheral edema	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	3 (0.2)	-0.1 (-0.3, 0.2)
Dizziness	4 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)	5 (0.9)	7 (1.3)	-0.4 (-1.7, 0.9)	9 (0.6)	13 (0.8)	-0.3 (-0.8, 0.3)
Fatigue	5 (0.5)	9 (0.9)	-0.4 (-1.1, 0.3)	2 (0.4)	3 (0.6)	-0.2 (-1.0, 0.6)	7 (0.4)	12 (0.8)	-0.3 (-0.9, 0.2)
Fall	5 (0.5)	11 (1.0)	-0.6 (-1.3, 0.2)	6 (1.1)	7 (1.3)	-0.2 (-1.5, 1.1)	11 (0.7)	18 (1.1)	-0.4 (-1.1, 0.2)
Hepatobiliary disorders (SOC)									
Hepatic failure	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	2 (0.4)	-0.2 (-0.8, 0.4)	3 (0.2)	3 (0.2)	0.0 (-0.3, 0.3)
Hepatic injury	23 (2.2)	36 (3.4)	-1.2 (-2.6, 0.2)	16 (3.0)	12 (2.3)	0.7 (-1.2, 2.6)	39 (2.5)	48 (3.0)	-0.6 (-1.7, 0.6)
Immune system disorders (SOC)									
Angioedema	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypersensitivity	7 (0.7)	10 (0.9)	-0.3 (-1.0, 0.5)	3 (0.6)	6 (1.1)	-0.6 (-1.7, 0.5)	10 (0.6)	16 (1.0)	-0.4 (-1.0, 0.3)
Infections and infestations (SOC)									
Purulent material	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Fungal infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Opportunistic infection	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Nasopharyngitis	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	2 (0.4)	6 (1.1)	-0.8 (-1.8, 0.3)	4 (0.3)	7 (0.4)	-0.2 (-0.6, 0.2)
Bacterial infection	8 (0.8)	19 (1.8)	-1.0 (-2.0, -0.1)*	5 (0.9)	10 (1.9)	-1.0 (-2.4, 0.4)	13 (0.8)	29 (1.8)	-1.0 (-1.8, -0.2)*
Pneumonia	6 (0.6)	21 (2.0)	-1.4 (-2.4, -0.5)*	4 (0.7)	7 (1.3)	-0.6 (-1.8, 0.6)	10 (0.6)	28 (1.8)	-1.1 (-1.9, -0.4)*
Viral infection	18 (1.7)	71 (6.7)	-5.0 (-6.7, -3.3)*	6 (1.1)	18 (3.4)	-2.3 (-4.1, -0.5)*	24 (1.5)	89 (5.6)	-4.1 (-5.4, -2.8)*
Metabolism and nutrition disorders (SOC)									
Lipid disorder	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)									
Arthralgia	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	3 (0.2)	0.1 (-0.2, 0.5)
Gout	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Myalgia	7 (0.7)	4 (0.4)	0.3 (-0.3, 0.9)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	8 (0.5)	7 (0.4)	0.1 (-0.4, 0.5)
Back pain	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	3 (0.6)	2 (0.4)	0.2 (-0.6, 1.0)	4 (0.3)	4 (0.3)	0.0 (-0.4, 0.4)
Fracture	0	2 (0.2)	-0.2 (-0.5, 0.1)	0	0	0 (0, 0)	0	2 (0.1)	-0.1 (-0.3, 0.0)
Rhabdomyolysis	1 (0.1)	5 (0.5)	-0.4 (-0.8, 0.1)	4 (0.7)	5 (0.9)	-0.2 (-1.3, 0.9)	5 (0.3)	10 (0.6)	-0.3 (-0.8, 0.2)

	EPIC-HR			EPIC-SR			Pooled		
System Organ Class FMQ (Broad)	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)
Nervous system disorders (SOC)									
Dysgeusia	48 (4.6)	1 (0.09)	4.5 (3.2, 5.8)*	32 (5.9)	2 (0.4)	5.5 (3.5, 7.6)*	80 (5.1)	3 (0.2)	4.9 (3.8, 6.0)*
Stroke TIA	2 (0.2)	0	0.2 (-0.1, 0.5)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	0	0.2 (-0.0, 0.4)
Confusional state	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Tremor	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Headache	12 (1.2)	13 (1.2)	-0.1 (-1.0, 0.9)	6 (1.1)	8 (1.5)	-0.4 (-1.8, 1.0)	18 (1.1)	21 (1.3)	-0.2 (-1.0, 0.6)
Syncope	4 (0.4)	9 (0.9)	-0.5 (-1.1, 0.2)	6 (1.1)	6 (1.1)	-0.0 (-1.3, 1.2)	10 (0.6)	15 (0.9)	-0.3 (-0.9, 0.3)
Somnolence	2 (0.2)	6 (0.6)	-0.4 (-0.9, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	2 (0.1)	7 (0.4)	-0.3 (-0.7, 0.1)
Psychiatric disorders (SOC)									
Arthritis	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	2 (0.4)	2 (0.4)	-0.0 (-0.7, 0.7)	6 (0.4)	5 (0.3)	0.1 (-0.3, 0.5)
Anxiety	4 (0.4)	3 (0.3)	0.1 (-0.4, 0.6)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)
Insomnia	2 (0.2)	2 (0.2)	0.0 (-0.4, 0.4)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Depression	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	2 (0.1)	1 (0.06)	0.1 (-0.2, 0.3)
Irritability	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Psychosis	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Parasomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Study agent abuse potential	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Renal and urinary disorders (SOC)									
Acute kidney injury	17 (1.6)	20 (1.9)	-0.3 (-1.4, 0.9)	7 (1.3)	4 (0.8)	0.5 (-0.7, 1.7)	24 (1.5)	24 (1.5)	0.0 (-0.9, 0.9)
Renal and urinary tract infection	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	3 (0.2)	4 (0.3)	-0.1 (-0.4, 0.3)
Urinary retention	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Reproductive system and breast disorders (SOC)									
Excessive menstrual bleeding	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abnormal uterine bleeding	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Respiratory, thoracic, and mediastinal disorders (SOC)									
Cough	8 (0.8)	6 (0.6)	0.2 (-0.5, 0.9)	0	3 (0.6)	-0.6 (-1.2, 0.1)	8 (0.5)	9 (0.6)	-0.1 (-0.6, 0.4)
Dyspnea	7 (0.7)	9 (0.9)	-0.2 (-0.9, 0.6)	3 (0.6)	3 (0.6)	-0.0 (-0.9, 0.9)	10 (0.6)	12 (0.8)	-0.1 (-0.7, 0.5)
Respiratory depression	2 (0.2)	8 (0.8)	-0.6 (-1.2, 0.0)	1 (0.2)	0	0.2 (-0.2, 0.5)	3 (0.2)	8 (0.5)	-0.3 (-0.7, 0.1)
Bronchospasm	8 (0.8)	10 (0.9)	-0.2 (-1.0, 0.6)	2 (0.4)	6 (1.1)	-0.8 (-1.8, 0.3)	10 (0.6)	16 (1.0)	-0.4 (-1.0, 0.3)
Respiratory failure	9 (0.9)	17 (1.6)	-0.7 (-1.7, 0.2)	4 (0.7)	3 (0.6)	0.2 (-0.8, 1.1)	13 (0.8)	20 (1.3)	-0.4 (-1.1, 0.3)
Pneumonitis	2 (0.2)	12 (1.1)	-0.9 (-1.6, -0.3)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	13 (0.8)	-0.6 (-1.1, -0.1)*

System Organ Class FMQ (Broad)	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)
Skin and subcutaneous tissue disorders (SOC)									
Pruritus	1 (0.1)	0	0.1 (-0.1, 0.3)	2 (0.4)	0	0.4 (-0.1, 0.9)	3 (0.2)	0	0.2 (-0.0, 0.4)
Urticaria	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	0	0	0 (0, 0)	3 (0.2)	5 (0.3)	-0.1 (-0.5, 0.2)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	3 (0.2)	-0.1 (-0.4, 0.1)
Rash	5 (0.5)	9 (0.9)	-0.4 (-1.1, 0.3)	0	0	0 (0, 0)	5 (0.3)	9 (0.6)	-0.3 (-0.7, 0.2)
Erythema	0	4 (0.4)	-0.4 (-0.8, -0.0)*	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	5 (0.3)	-0.3 (-0.6, 0.1)
Vascular disorders (SOC)									
Hypotension	3 (0.3)	5 (0.5)	-0.2 (-0.7, 0.3)	5 (0.9)	1 (0.2)	0.7 (-0.2, 1.6)	8 (0.5)	6 (0.4)	0.1 (-0.3, 0.6)
Hemorrhage	3 (0.3)	3 (0.3)	0.0 (-0.5, 0.5)	2 (0.4)	1 (0.2)	0.2 (-0.5, 0.8)	5 (0.3)	4 (0.3)	0.1 (-0.3, 0.4)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs. placebo.
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Table 152 includes the AEs considered by the investigator to be related to study drug in EPIC-HR and EPIC-SR. These AEs were previously discussed in Section 7.6.1.5.

Table 152. Patients With Adverse Events[1] Assessed by Investigator as Treatment-Related, Safety Population, EPIC-HR and EPIC-SR[2]

Preferred Term	EPIC-HR PAXLOVID N=1038 n (%)	EPIC-HR Placebo N=1053 n (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n (%)	EPIC-SR Placebo N=528 n (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n (%)	Pooled Placebo N=1581 n (%)	Pooled Risk Difference (%) (95% CI)[3]
Any treatment-related AE	67 (6.5)	39 (3.7)	2.8 (0.9, 4.6)*	61 (11.3)	28 (5.3)	6.0 (2.7, 9.3)*	128 (8.1)	67 (4.2)	3.9 (2.2, 5.5)*
Dysgeusia	36 (3.5)	0	3.5 (2.4, 4.6)*	24 (4.4)	1 (0.2)	4.3 (2.5, 6.0)*	60 (3.8)	1 (0.06)	3.7 (2.8, 4.7)*
Diarrhea	11 (1.1)	2 (0.2)	0.9 (0.2, 1.5)*	12 (2.2)	8 (1.5)	0.7 (-0.9, 2.3)	23 (1.5)	10 (0.6)	0.8 (0.1, 1.5)*
AST increased	4 (0.4)	0	0.4 (0.0, 0.8)*	3 (0.6)	0	0.6 (-0.1, 1.2)	7 (0.4)	0	0.4 (0.1, 0.8)*
ALT increased	5 (0.5)	2 (0.2)	0.3 (-0.2, 0.8)	4 (0.7)	1 (0.2)	0.6 (-0.3, 1.4)	9 (0.6)	3 (0.2)	0.4 (-0.0, 0.8)
Product after taste	3 (0.3)	0	0.3 (-0.0, 0.6)	2 (0.4)	0	0.4 (-0.1, 0.9)	5 (0.3)	0	0.3 (0.0, 0.6)*
Dyspepsia	3 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)	2 (0.4)	0	0.4 (-0.1, 0.9)	5 (0.3)	2 (0.1)	0.2 (-0.1, 0.5)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Vomiting	6 (0.6)	4 (0.4)	0.2 (-0.4, 0.8)	4 (0.7)	4 (0.8)	-0.0 (-1.1, 1.0)	10 (0.6)	8 (0.5)	0.1 (-0.4, 0.7)
Blood TSH decreased	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Chest discomfort	1 (0.1)	0	0.1 (-0.1, 0.3)	1 (0.2)	0	0.2 (-0.2, 0.5)	2 (0.1)	0	0.1 (-0.0, 0.3)
Myalgia	2 (0.2)	0	0.2 (-0.1, 0.5)	0	0	0 (0, 0)	2 (0.1)	0	0.1 (-0.0, 0.3)
Nausea	8 (0.8)	9 (0.9)	-0.1 (-0.9, 0.7)	11 (2.0)	9 (1.7)	0.3 (-1.3, 2.0)	19 (1.2)	18 (1.1)	0.1 (-0.7, 0.8)
Dizziness	2 (0.2)	1 (0.09)	0.1 (-0.2, 0.4)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	3 (0.2)	2 (0.1)	0.1 (-0.2, 0.3)
Abdominal discomfort	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Anxiety	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Aphthous ulcer	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood bilirubin increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood fibrinogen increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Blood LDH increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
CRP increased	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Chromaturia	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Colitis	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Decreased appetite	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Feces soft	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
GERD	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hiccups	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypertension	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Hypothyroidism	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oral discomfort	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Oropharyngeal pain	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Paresthesia	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Parosmia	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Pollakiuria	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
Rash maculo-papular	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Skin exfoliation	1 (0.1)	0	0.1 (-0.1, 0.3)	0	0	0 (0, 0)	1 (0.06)	0	0.1 (-0.1, 0.2)
Taste disorder	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	0	0.1 (-0.1, 0.2)
APTT prolonged	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Alopecia	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Blood CPK increased	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Dyspnea	1 (0.1)	0	0.1 (-0.1, 0.3)	0	1 (0.2)	-0.2 (-0.6, 0.2)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Gastritis	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Palpitations	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Thyroxine free increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	1 (0.2)	0	0.2 (-0.2, 0.5)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Vertigo	1 (0.1)	1 (0.09)	0.0 (-0.3, 0.3)	0	0	0 (0, 0)	1 (0.06)	1 (0.06)	0.0 (-0.2, 0.2)
Rash	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	0	0 (0, 0)	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.2)
Abdominal distension	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Abdominal pain	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Acne	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Anterograde amnesia	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Asthenia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Blood glucose increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Confusional state	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Dehydration	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Eosinophil count increased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Erythema	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Fibrin D dimer increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Flatulence	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Haptoglobin increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypersomnia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hypoesthesia	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Migraine	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Orthostatic hypotension	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pain in extremity	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Peripheral swelling	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Platelet count decreased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Pyrexia	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	0	0 (0, 0)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Thyroxine increased	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	1 (0.06)	-0.1 (-0.2, 0.1)
Hepatic enzyme increased	0	1 (0.09)	-0.1 (-0.3, 0.1)	0	1 (0.2)	-0.2 (-0.6, 0.2)	0	2 (0.1)	-0.1 (-0.3, 0.0)

	EPIC-HR			EPIC-SR			Pooled		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)	Risk Difference (%) (95% CI)[3]
Blood TSH increased	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	1 (0.2)	3 (0.6)	-0.4 (-1.1, 0.4)	2 (0.1)	5 (0.3)	-0.2 (-0.5, 0.1)
Abdominal pain upper	1 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)	0	2 (0.4)	-0.4 (-0.9, 0.1)	1 (0.06)	4 (0.3)	-0.2 (-0.5, 0.1)
Headache	1 (0.1)	3 (0.3)	-0.2 (-0.6, 0.2)	0	3 (0.6)	-0.6 (-1.2, 0.1)	1 (0.06)	6 (0.4)	-0.3 (-0.6, 0.0)

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CI, confidence interval; CPK, creatine phosphokinase; CRP, C-reactive protein; GERD, gastroesophageal reflux disease; LDH, lactate dehydrogenase; N, number of patients in treatment arm; n, number of patients with adverse event; TSH, thyroid stimulating hormone

17.5. Laboratory Findings, EPIC-HR and EPIC-SR

Table 153, Table 154, and Table 155 describe laboratory outliers assessed by the Safety Standard & Figures Integrated Guide (August 2022). An overview was previously provided in Section 7.6.1.6.

Reference ID: 5179402

Table 153. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)[3]
Sodium, low (mEq/L)									
Level 1 (<132)	28/991 (2.8)	30/999 (3.0)	-0.2 (-1.7, 1.3)	14/524 (2.7)	8/510 (1.6)	1.1 (-0.6, 2.9)	42/1515 (2.8)	38/1509 (2.5)	0.3 (-0.9, 1.4)
Level 2 (<130)	4/991 (0.4)	11/999 (1.1)	-0.7 (-1.5, 0.1)	4/524 (0.8)	2/510 (0.4)	0.4 (-0.6, 1.3)	8/1515 (0.5)	13/1509 (0.9)	-0.3 (-0.9, 0.3)
Level 3 (<125)	0/991 (0)	0/999 (0)	0 (0, 0)	1/524 (0.2)	0/510 (0)	0.2 (-0.2, 0.6)	1/1515 (0.07)	0/1509 (0)	0.1 (-0.1, 0.2)
Sodium, high (mEq/L)									
Level 1 (>150)	2/991 (0.2)	1/999 (0.1)	0.1 (-0.2, 0.4)	2/524 (0.4)	0/510 (0)	0.4 (-0.1, 0.9)	4/1515 (0.3)	1/1509 (0.07)	0.2 (-0.1, 0.5)
Level 2 (>155)	1/991 (0.1)	0/999 (0)	0.1 (-0.1, 0.3)	1/524 (0.2)	0/510 (0)	0.2 (-0.2, 0.6)	2/1515 (0.1)	0/1509 (0)	0.1 (-0.1, 0.3)
Level 3 (>160)	0/991 (0)	0/999 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1515 (0)	0/1509 (0)	0 (0, 0)
Potassium, low (mEq/L)									
Level 1 (<3.6)	76/985 (7.7)	65/1000 (6.5)	1.2 (-1.0, 3.5)	24/519 (4.6)	17/509 (3.3)	1.3 (-1.1, 3.7)	100/1504 (6.6)	82/1509 (5.4)	1.2 (-0.5, 2.9)
Level 2 (<3.4)	29/985 (2.9)	19/1000 (1.9)	1.0 (-0.3, 2.4)	7/519 (1.3)	3/509 (0.6)	0.8 (-0.4, 2.0)	36/1504 (2.4)	22/1509 (1.5)	0.9 (-0.0, 1.9)
Level 3 (<3)	3/985 (0.3)	5/1000 (0.5)	-0.2 (-0.8, 0.4)	1/519 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	4/1504 (0.3)	5/1509 (0.3)	-0.1 (-0.5, 0.3)
Potassium, high (mEq/L)									
Level 1 (>5.5)	24/985 (2.4)	24/1000 (2.4)	0.0 (-1.3, 1.4)	8/519 (1.5)	16/509 (3.1)	-1.6 (-3.5, 0.2)	32/1504 (2.1)	40/1509 (2.7)	-0.5 (-1.6, 0.6)
Level 2 (>6)	1/985 (0.1)	5/1000 (0.5)	-0.4 (-0.9, 0.1)	1/519 (0.2)	3/509 (0.6)	-0.4 (-1.2, 0.4)	2/1504 (0.1)	8/1509 (0.5)	-0.4 (-0.8, 0.0)
Level 3 (>6.5)	0/985 (0)	1/1000 (0.1)	-0.1 (-0.3, 0.1)	0/519 (0)	2/509 (0.4)	-0.4 (-0.9, 0.2)	0/1504 (0)	3/1509 (0.2)	-0.2 (-0.4, 0.0)
Chloride, low (mEq/L)									
Level 1 (<95)	84/991 (8.5)	82/998 (8.2)	0.3 (-2.2, 2.7)	31/524 (5.9)	16/509 (3.1)	2.8 (0.2, 5.3)	115/1515 (7.6)	98/1507 (6.5)	1.1 (-0.7, 2.9)
Level 2 (<88)	2/991 (0.2)	4/998 (0.4)	-0.2 (-0.7, 0.3)	4/524 (0.8)	0/509 (0)	0.8 (0.0, 1.5)	6/1515 (0.4)	4/1507 (0.3)	0.1 (-0.3, 0.5)
Level 3 (<80)	0/991 (0)	0/998 (0)	0 (0, 0)	1/524 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	1/1515 (0.07)	0/1507 (0)	0.1 (-0.1, 0.2)
Chloride, high (mEq/L)									
Level 1 (>108)	8/991 (0.8)	12/998 (1.2)	-0.4 (-1.3, 0.5)	6/524 (1.1)	1/509 (0.2)	0.9 (-0.0, 1.9)	14/1515 (0.9)	13/1507 (0.9)	0.1 (-0.6, 0.7)
Level 2 (>112)	0/991 (0)	0/998 (0)	0 (0, 0)	0/524 (0)	0/509 (0)	0 (0, 0)	0/1515 (0)	0/1507 (0)	0 (0, 0)
Level 3 (>115)	0/991 (0)	0/998 (0)	0 (0, 0)	0/524 (0)	0/509 (0)	0 (0, 0)	0/1515 (0)	0/1507 (0)	0 (0, 0)
Bicarbonate, low (mEq/L)									
Level 1 (<20)	169/989 (17.1)	157/997 (15.7)	1.3 (-1.9, 4.6)	70/519 (13.5)	79/506 (15.6)	-2.1 (-6.4, 2.2)	239/1508 (15.8)	236/1503 (15.7)	0.1 (-2.5, 2.8)
Level 2 (<18)	45/989 (4.6)	56/997 (5.6)	-1.1 (-3.0, 0.9)	17/519 (3.3)	21/506 (4.2)	-0.9 (-3.2, 1.4)	62/1508 (4.1)	77/1503 (5.1)	-1.0 (-2.5, 0.5)
Level 3 (<15)	2/989 (0.2)	9/997 (0.9)	-0.7 (-1.4, -0.1)	2/519 (0.4)	1/506 (0.2)	0.2 (-0.5, 0.8)	4/1508 (0.3)	10/1503 (0.7)	-0.4 (-0.9, 0.1)
Bicarbonate, high (mEq/L)									
Level 3 (>30)	11/989 (1.1)	16/997 (1.6)	-0.5 (-1.5, 0.5)	5/519 (1.0)	4/506 (0.8)	0.2 (-1.0, 1.3)	16/1508 (1.1)	20/1503 (1.3)	-0.3 (-1.0, 0.5)
Glucose, low (mg/dL)									
Level 1 (<70)	52/987 (5.3)	54/997 (5.4)	-0.1 (-2.1, 1.8)	38/517 (7.4)	27/506 (5.3)	2.0 (-1.0, 5.0)	90/1504 (6.0)	81/1503 (5.4)	0.6 (-1.1, 2.3)
Level 2 (<54)	6/987 (0.6)	4/997 (0.4)	0.2 (-0.4, 0.8)	2/517 (0.4)	4/506 (0.8)	-0.4 (-1.3, 0.5)	8/1504 (0.5)	8/1503 (0.5)	-0.0 (-0.5, 0.5)
Level 3 (<40)	2/987 (0.2)	0/997 (0)	0.2 (-0.1, 0.5)	0/517 (0)	0/506 (0)	0 (0, 0)	2/1504 (0.1)	0/1503 (0)	0.1 (-0.1, 0.3)
Glucose, fasting, high (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA

	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)[3]
Glucose, random, high (mg/dL)									
Level 2 (≥200)	75/987 (7.6)	75/997 (7.5)	0.1 (-2.3, 2.4)	19/517 (3.7)	22/506 (4.3)	-0.7 (-3.1, 1.7)	94/1504 (6.2)	97/1503 (6.5)	-0.2 (-1.9, 1.5)
Level 3 (>250)	43/987 (4.4)	44/997 (4.4)	-0.1 (-1.9, 1.7)	9/517 (1.7)	17/506 (3.4)	-1.6 (-3.6, 0.3)	52/1504 (3.5)	61/1503 (4.1)	-0.6 (-2.0, 0.8)
Calcium, low (mg/dL)									
Level 1 (<8.4)	40/985 (4.1)	61/999 (6.1)	-2.0 (-4.0, -0.1)	17/520 (3.3)	23/509 (4.5)	-1.2 (-3.6, 1.1)	57/1505 (3.8)	84/1508 (5.6)	-1.8 (-3.3, -0.3)
Level 2 (<8)	16/985 (1.6)	19/999 (1.9)	-0.3 (-1.4, 0.9)	5/520 (1.0)	12/509 (2.4)	-1.4 (-3.0, 0.2)	21/1505 (1.4)	31/1508 (2.1)	-0.7 (-1.6, 0.3)
Level 3 (<7.5)	5/985 (0.5)	7/999 (0.7)	-0.2 (-0.9, 0.5)	4/520 (0.8)	7/509 (1.4)	-0.6 (-1.9, 0.7)	9/1505 (0.6)	14/1508 (0.9)	-0.3 (-1.0, 0.3)
Calcium, high (mg/dL)									
Level 1 (>10.5)	23/985 (2.3)	14/999 (1.4)	0.9 (-0.3, 2.1)	5/520 (1.0)	3/509 (0.6)	0.4 (-0.7, 1.4)	28/1505 (1.9)	17/1508 (1.1)	0.7 (-0.1, 1.6)
Level 2 (>11)	1/985 (0.1)	3/999 (0.3)	-0.2 (-0.6, 0.2)	0/520 (0)	1/509 (0.2)	-0.2 (-0.6, 0.2)	1/1505 (0.07)	4/1508 (0.3)	-0.2 (-0.5, 0.1)
Level 3 (>12)	0/985 (0)	0/999 (0)	0 (0, 0)	0/520 (0)	0/509 (0)	0 (0, 0)	0/1505 (0)	0/1508 (0)	0 (0, 0)
Magnesium, low (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)									
Level 1 (<6)	35/989 (3.5)	34/997 (3.4)	0.1 (-1.5, 1.7)	5/519 (1.0)	7/506 (1.4)	-0.4 (-1.7, 0.9)	40/1508 (2.7)	41/1503 (2.7)	-0.1 (-1.2, 1.1)
Level 2 (<5.4)	2/989 (0.2)	4/997 (0.4)	-0.2 (-0.7, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	2/1508 (0.1)	4/1503 (0.3)	-0.1 (-0.5, 0.2)
Level 3 (<5)	1/989 (0.1)	0/997 (0)	0.1 (-0.1, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1508 (0.07)	0/1503 (0)	0.1 (-0.1, 0.2)
Albumin, low (g/dL)									
Level 1 (<3.1)	2/992 (0.2)	4/1001 (0.4)	-0.2 (-0.7, 0.3)	0/524 (0)	0/510 (0)	0 (0, 0)	2/1516 (0.1)	4/1511 (0.3)	-0.1 (-0.4, 0.2)
Level 2 (<2.5)	0/992 (0)	0/1001 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1516 (0)	0/1511 (0)	0 (0, 0)
Level 3 (<2)	0/992 (0)	0/1001 (0)	0 (0, 0)	0/524 (0)	0/510 (0)	0 (0, 0)	0/1516 (0)	0/1511 (0)	0 (0, 0)
CPK, high (U/L)									
Level 1 (>3X ULN)	31/990 (3.1)	27/997 (2.7)	0.4 (-1.1, 1.9)	17/519 (3.3)	17/506 (3.4)	-0.1 (-2.3, 2.1)	48/1509 (3.2)	44/1503 (2.9)	0.3 (-1.0, 1.5)
Level 2 (>5X ULN)	11/990 (1.1)	12/997 (1.2)	-0.1 (-1.0, 0.8)	5/519 (1.0)	6/506 (1.2)	-0.2 (-1.5, 1.0)	16/1509 (1.1)	18/1503 (1.2)	-0.1 (-0.9, 0.6)
Level 3 (>10X ULN)	5/990 (0.5)	4/997 (0.4)	0.1 (-0.5, 0.7)	3/519 (0.6)	3/506 (0.6)	-0.0 (-0.9, 0.9)	8/1509 (0.5)	7/1503 (0.5)	0.1 (-0.4, 0.6)
Amylase, high (U/L)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)									
Missing	NA	NA	NA	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)									
Level 1 (>23)	64/991 (6.5)	77/1000 (7.7)	-1.2 (-3.5, 1.0)	16/524 (3.1)	20/509 (3.9)	-0.9 (-3.1, 1.4)	80/1515 (5.3)	97/1509 (6.4)	-1.1 (-2.8, 0.5)
Level 2 (>27)	37/991 (3.7)	34/1000 (3.4)	0.3 (-1.3, 2.0)	6/524 (1.1)	6/509 (1.2)	-0.0 (-1.3, 1.3)	43/1515 (2.8)	40/1509 (2.7)	0.2 (-1.0, 1.4)
Level 3 (>31)	16/991 (1.6)	21/1000 (2.1)	-0.5 (-1.7, 0.7)	2/524 (0.4)	3/509 (0.6)	-0.2 (-1.1, 0.6)	18/1515 (1.2)	24/1509 (1.6)	-0.4 (-1.2, 0.4)

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/Nw (%)	EPIC-HR Placebo N=1053 n/Nw (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/Nw (%)	EPIC-SR Placebo N=528 n/Nw (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/Nw (%)	Pooled Placebo N=1581 n/Nw (%)	Pooled Risk Difference (%) (95% CI)[3]
Creatinine, high (mg/dL)									
Level 1 (≥1.5X baseline)	37/969 (3.8)	28/985 (2.8)	1.0 (-0.6, 2.6)	22/508 (4.3)	15/497 (3.0)	1.3 (-1.0, 3.6)	59/1477 (4.0)	43/1482 (2.9)	1.1 (-0.2, 2.4)
Level 2 (≥2X baseline)	4/969 (0.4)	3/985 (0.3)	0.1 (-0.4, 0.6)	4/508 (0.8)	3/497 (0.6)	0.2 (-0.8, 1.2)	8/1477 (0.5)	6/1482 (0.4)	0.1 (-0.4, 0.6)
Level 3 (≥3X baseline)	0/969 (0)	0/985 (0)	0 (0, 0)	0/508 (0)	0/497 (0)	0 (0, 0)	0/1477 (0)	0/1482 (0)	0 (0, 0)
eGFR, low (ml/min/1.73 m2)									
Level 1 (≥25% decrease)	46/969 (4.7)	39/985 (4.0)	0.8 (-1.0, 2.6)	22/508 (4.3)	22/497 (4.4)	-0.1 (-2.6, 2.4)	68/1477 (4.6)	61/1482 (4.1)	0.5 (-1.0, 2.0)
Level 2 (≥50% decrease)	2/969 (0.2)	2/985 (0.2)	0.0 (-0.4, 0.4)	1/508 (0.2)	1/497 (0.2)	-0.0 (-0.6, 0.5)	3/1477 (0.2)	3/1482 (0.2)	0.0 (-0.3, 0.3)
Level 3 (≥75% decrease)	0/969 (0)	0/985 (0)	0 (0, 0)	0/508 (0)	0/497 (0)	0 (0, 0)	0/1477 (0)	0/1482 (0)	0 (0, 0)

Source: adlb.xpt; Software: R.
Note: Glucose values for hyperglycemia do not follow a nested format l ke the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Note: Participants enrolled in Trial EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in Trial EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 154. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
ALP, high (U/L)									
Level 1 (>1.5X ULN)	5/986 (0.5)	11/999 (1.1)	-0.6 (-1.4, 0.2)	3/520 (0.6)	4/509 (0.8)	-0.2 (-1.2, 0.8)	8/1506 (0.5)	15/1508 (1.0)	-0.5 (-1.1, 0.2)
Level 2 (>2X ULN)	1/986 (0.1)	4/999 (0.4)	-0.3 (-0.7, 0.1)	1/520 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	2/1506 (0.1)	4/1508 (0.3)	-0.1 (-0.5, 0.2)
Level 3 (>3X ULN)	0/986 (0)	2/999 (0.2)	-0.2 (-0.5, 0.1)	1/520 (0.2)	0/509 (0)	0.2 (-0.2, 0.6)	1/1506 (0.07)	2/1508 (0.1)	-0.1 (-0.3, 0.2)
ALT, high (U/L)									
Level 1 (>3X ULN)	35/990 (3.5)	45/997 (4.5)	-1.0 (-2.7, 0.7)	11/519 (2.1)	12/506 (2.4)	-0.3 (-2.1, 1.6)	46/1509 (3.0)	57/1503 (3.8)	-0.7 (-2.0, 0.6)
Level 2 (>5X ULN)	6/990 (0.6)	14/997 (1.4)	-0.8 (-1.7, 0.1)	3/519 (0.6)	3/506 (0.6)	-0.0 (-0.9, 0.9)	9/1509 (0.6)	17/1503 (1.1)	-0.5 (-1.2, 0.1)
Level 3 (>10X ULN)	0/990 (0)	1/997 (0.1)	-0.1 (-0.3, 0.1)	1/519 (0.2)	0/506 (0)	0.2 (-0.2, 0.6)	1/1509 (0.07)	1/1503 (0.07)	-0.0 (-0.2, 0.2)

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
AST, high (U/L)									
Level 1 (>3X ULN)	14/990 (1.4)	14/996 (1.4)	0.0 (-1.0, 1.0)	4/519 (0.8)	2/506 (0.4)	0.4 (-0.6, 1.3)	18/1509 (1.2)	16/1502 (1.1)	0.1 (-0.6, 0.9)
Level 2 (>5X ULN)	5/990 (0.5)	5/996 (0.5)	0.0 (-0.6, 0.6)	2/519 (0.4)	0/506 (0)	0.4 (-0.1, 0.9)	7/1509 (0.5)	5/1502 (0.3)	0.1 (-0.3, 0.6)
Level 3 (>10X ULN)	1/990 (0.1)	1/996 (0.1)	0.0 (-0.3, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1509 (0.07)	1/1502 (0.07)	-0.0 (-0.2, 0.2)
Bilirubin, total, high (mg/dL)									
Level 1 (>1.5X ULN)	5/990 (0.5)	2/997 (0.2)	0.3 (-0.2, 0.8)	2/519 (0.4)	5/506 (1.0)	-0.6 (-1.6, 0.4)	7/1509 (0.5)	7/1503 (0.5)	-0.0 (-0.5, 0.5)
Level 2 (>2X ULN)	2/990 (0.2)	0/997 (0)	0.2 (-0.1, 0.5)	1/519 (0.2)	3/506 (0.6)	-0.4 (-1.2, 0.4)	3/1509 (0.2)	3/1503 (0.2)	-0.0 (-0.3, 0.3)
Level 3 (>3X ULN)	1/990 (0.1)	0/997 (0)	0.1 (-0.1, 0.3)	0/519 (0)	0/506 (0)	0 (0, 0)	1/1509 (0.07)	0/1503 (0)	0.1 (-0.1, 0.2)

Source: adlb.xpt; Software: R.
Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 155. Patients With One or More Hematology Analyte Values Exceeding Specified Levels[1], Safety Population, EPIC-HR and EPIC-SR[2]

Laboratory Parameter	EPIC-HR PAXLOVID N=1038 n/N_w (%)	EPIC-HR Placebo N=1053 n/N_w (%)	EPIC-HR Risk Difference (%) (95% CI)	EPIC-SR PAXLOVID N=540 n/N_w (%)	EPIC-SR Placebo N=528 n/N_w (%)	EPIC-SR Risk Difference (%) (95% CI)	Pooled PAXLOVID N=1578 n/N_w (%)	Pooled Placebo N=1581 n/N_w (%)	Pooled Risk Difference (%) (95% CI)[3]
Complete Blood Count									
WBC, low (cells/uL)									
Level 1 (<3500)	40/873 (4.6)	81/890 (9.1)	-4.5 (-6.9, -2.2)	18/461 (3.9)	33/446 (7.4)	-3.5 (-6.5, -0.5)	58/1334 (4.3)	114/1336 (8.5)	-4.2 (-6.0, -2.3)
Level 2 (<3000)	14/873 (1.6)	39/890 (4.4)	-2.8 (-4.4, -1.2)	8/461 (1.7)	13/446 (2.9)	-1.2 (-3.1, 0.8)	22/1334 (1.6)	52/1336 (3.9)	-2.2 (-3.5, -1.0)
Level 3 (<1000)	0/873 (0)	1/890 (0.1)	-0.1 (-0.3, 0.1)	0/461 (0)	0/446 (0)	0 (0, 0)	0/1334 (0)	1/1336 (0.07)	-0.1 (-0.2, 0.1)
WBC, high (cells/uL)									
Level 1 (>10800)	122/873 (14.0)	98/890 (11.0)	3.0 (-0.1, 6.0)	35/461 (7.6)	29/446 (6.5)	1.1 (-2.2, 4.4)	157/1334 (11.8)	127/1336 (9.5)	2.3 (-0.1, 4.6)
Level 2 (>13000)	48/873 (5.5)	33/890 (3.7)	1.8 (-0.2, 3.7)	12/461 (2.6)	8/446 (1.8)	0.8 (-1.1, 2.7)	60/1334 (4.5)	41/1336 (3.1)	1.4 (-0.0, 2.9)
Level 3 (>15000)	18/873 (2.1)	15/890 (1.7)	0.4 (-0.9, 1.6)	3/461 (0.7)	5/446 (1.1)	-0.5 (-1.7, 0.8)	21/1334 (1.6)	20/1336 (1.5)	0.1 (-0.9, 1.0)
Hemoglobin, low (g/dL)									
Level 2 (>1.5 dec. from BL)	85/586 (14.5)	109/630 (17.3)	-2.8 (-6.9, 1.3)	41/314 (13.1)	40/316 (12.7)	0.4 (-4.8, 5.6)	126/900 (14.0)	149/946 (15.8)	-1.8 (-5.0, 1.5)
Level 3 (>2 dec. from BL)	43/586 (7.3)	49/630 (7.8)	-0.4 (-3.4, 2.5)	15/314 (4.8)	14/316 (4.4)	0.3 (-2.9, 3.6)	58/900 (6.4)	63/946 (6.7)	-0.2 (-2.5, 2.0)
Hemoglobin, high (g/dL)									
Level 2 (>2 inc. from BL)	6/586 (1.0)	13/630 (2.1)	-1.0 (-2.4, 0.3)	1/314 (0.3)	4/316 (1.3)	-0.9 (-2.3, 0.4)	7/900 (0.8)	17/946 (1.8)	-1.0 (-2.0, 0.0)
Level 3 (>3 inc. from BL)	2/586 (0.3)	3/630 (0.5)	-0.1 (-0.9, 0.6)	0/314 (0)	0/316 (0)	0 (0, 0)	2/900 (0.2)	3/946 (0.3)	-0.1 (-0.6, 0.4)

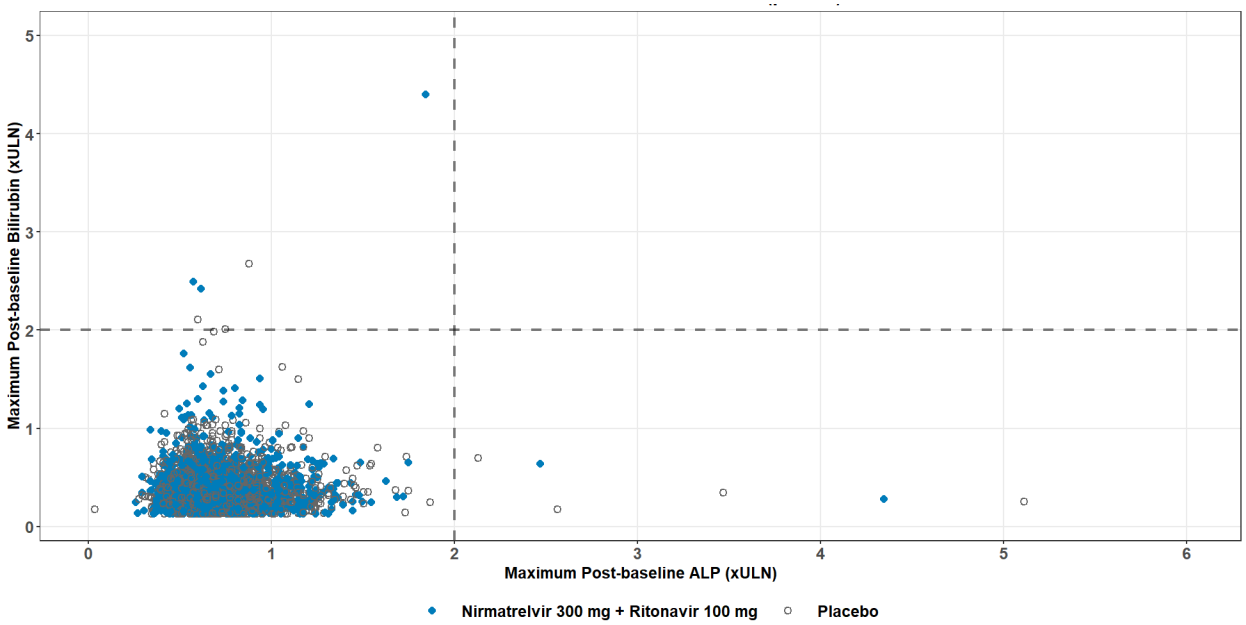
	EPIC-HR			EPIC-SR			Pooled		
Laboratory Parameter	**PAXLOVID N=1038 n/N_w (%)**	**Placebo N=1053 n/N_w (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=540 n/N_w (%)**	**Placebo N=528 n/N_w (%)**	**Risk Difference (%) (95% CI)**	**PAXLOVID N=1578 n/N_w (%)**	**Placebo N=1581 n/N_w (%)**	**Risk Difference (%) (95% CI)[3]**
Platelets, low (cells/uL)									
Level 1 (<140000)	28/864 (3.2)	40/884 (4.5)	-1.3 (-3.1, 0.5)	11/456 (2.4)	13/439 (3.0)	-0.5 (-2.7, 1.6)	39/1320 (3.0)	53/1323 (4.0)	-1.1 (-2.4, 0.3)
Level 2 (<125000)	12/864 (1.4)	23/884 (2.6)	-1.2 (-2.5, 0.1)	6/456 (1.3)	6/439 (1.4)	-0.1 (-1.6, 1.5)	18/1320 (1.4)	29/1323 (2.2)	-0.8 (-1.8, 0.2)
Level 3 (<100000)	1/864 (0.1)	6/884 (0.7)	-0.6 (-1.1, 0.0)	1/456 (0.2)	2/439 (0.5)	-0.2 (-1.0, 0.5)	2/1320 (0.2)	8/1323 (0.6)	-0.5 (-0.9, 0.0)
WBC Differential									
Lymphocytes, low (cells/uL)									
Level 1 (<1000)	68/870 (7.8)	101/882 (11.5)	-3.6 (-6.4, -0.9)	16/457 (3.5)	21/441 (4.8)	-1.3 (-3.9, 1.3)	84/1327 (6.3)	122/1323 (9.2)	-2.9 (-4.9, -0.9)
Level 2 (<750)	22/870 (2.5)	46/882 (5.2)	-2.7 (-4.5, -0.9)	5/457 (1.1)	7/441 (1.6)	-0.5 (-2.0, 1.0)	27/1327 (2.0)	53/1323 (4.0)	-2.0 (-3.3, -0.7)
Level 3 (<500)	7/870 (0.8)	10/882 (1.1)	-0.3 (-1.2, 0.6)	1/457 (0.2)	3/441 (0.7)	-0.5 (-1.3, 0.4)	8/1327 (0.6)	13/1323 (1.0)	-0.4 (-1.1, 0.3)
Lymphocytes, high (cells/uL)									
Level 1 (>4000)	21/870 (2.4)	19/882 (2.2)	0.3 (-1.1, 1.7)	7/457 (1.5)	3/441 (0.7)	0.9 (-0.5, 2.2)	28/1327 (2.1)	22/1323 (1.7)	0.4 (-0.6, 1.5)
Level 2 (>10000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Level 3 (>20000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Neutrophils, low (cells/uL)									
Level 1 (<2000)	110/866 (12.7)	138/881 (15.7)	-3.0 (-6.2, 0.3)	58/455 (12.7)	73/439 (16.6)	-3.9 (-8.5, 0.8)	168/1321 (12.7)	211/1320 (16.0)	-3.3 (-5.9, -0.6)
Level 2 (<1000)	8/866 (0.9)	15/881 (1.7)	-0.8 (-1.8, 0.3)	5/455 (1.1)	8/439 (1.8)	-0.7 (-2.3, 0.9)	13/1321 (1.0)	23/1320 (1.7)	-0.8 (-1.6, 0.1)
Level 3 (<500)	1/866 (0.1)	2/881 (0.2)	-0.1 (-0.5, 0.3)	0/455 (0)	1/439 (0.2)	-0.2 (-0.7, 0.2)	1/1321 (0.08)	3/1320 (0.2)	-0.2 (-0.4, 0.1)
Eosinophils, high (cells/uL)									
Level 1 (>650)	24/870 (2.8)	16/882 (1.8)	0.9 (-0.5, 2.3)	2/457 (0.4)	7/441 (1.6)	-1.1 (-2.5, 0.2)	26/1327 (2.0)	23/1323 (1.7)	0.2 (-0.8, 1.2)
Level 2 (>1500)	2/870 (0.2)	2/882 (0.2)	0.0 (-0.4, 0.5)	0/457 (0)	1/441 (0.2)	-0.2 (-0.7, 0.2)	2/1327 (0.2)	3/1323 (0.2)	-0.1 (-0.4, 0.3)
Level 3 (>5000)	0/870 (0)	0/882 (0)	0 (0, 0)	0/457 (0)	0/441 (0)	0 (0, 0)	0/1327 (0)	0/1323 (0)	0 (0, 0)
Coagulation Studies									
PT, high (sec)									
Level 1 (>1.1X ULN)	92/931 (9.9)	106/942 (11.3)	-1.4 (-4.2, 1.4)	14/513 (2.7)	12/498 (2.4)	0.3 (-1.6, 2.3)	106/1444 (7.3)	118/1440 (8.2)	-0.9 (-2.8, 1.1)
Level 2 (>1.3X ULN)	24/931 (2.6)	22/942 (2.3)	0.2 (-1.2, 1.6)	4/513 (0.8)	3/498 (0.6)	0.2 (-0.8, 1.2)	28/1444 (1.9)	25/1440 (1.7)	0.2 (-0.8, 1.2)
Level 3 (>1.5X ULN)	19/931 (2.0)	7/942 (0.7)	1.3 (0.2, 2.4)	3/513 (0.6)	2/498 (0.4)	0.2 (-0.7, 1.0)	22/1444 (1.5)	9/1440 (0.6)	0.9 (0.1, 1.7)
PTT, high (sec)									
Level 1 (>1X ULN)	327/928 (35.2)	336/942 (35.7)	-0.4 (-4.8, 3.9)	191/513 (37.2)	180/498 (36.1)	1.1 (-4.9, 7.0)	518/1441 (35.9)	516/1440 (35.8)	0.1 (-3.4, 3.6)
Level 2 (>1.21X ULN)	75/928 (8.1)	90/942 (9.6)	-1.5 (-4.0, 1.1)	28/513 (5.5)	50/498 (10.0)	-4.6 (-7.9, -1.3)	103/1441 (7.1)	140/1440 (9.7)	-2.6 (-4.6, -0.5)
Level 3 (>1.41X ULN)	32/928 (3.4)	32/942 (3.4)	0.1 (-1.6, 1.7)	9/513 (1.8)	9/498 (1.8)	-0.1 (-1.7, 1.6)	41/1441 (2.8)	41/1440 (2.8)	-0.0 (-1.2, 1.2)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in Trial EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in Trial EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: BL, baseline; CI, confidence interval; dec, decrease; inc, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, White blood cells

17.6. Assessment of Drug-Induced Liver Injury, EPIC-HR and EPIC-SR

As previously discussed in Section 7.6.1.7, there were two cases of potential hepatocellular drug induced liver injury (DILI) in PAXLOVID group in the EPIC-HR and EPIC-SR trials (one in each). As demonstrated in Figure 64 and Table 156, there were no cases of cholestatic drug-induced liver injury.

Figure 64. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-HR and EPIC-SR



Source: adlb.xpt; Software: R.
Note: Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the post-baseline period.
Note: A potential cholestatic DILI case (red circled) was defined as having a maximum post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after post-baseline ALP became equal to or exceeding 2X ULN.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 156. Patients in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR		EPIC-SR		Pooled	
Quadrant	PAXLOVID N=1038 n/N_w (%)	Placebo N=1053 n/N_w (%)	PAXLOVID N=540 n/N_w (%)	Placebo N=528 n/N_w (%)	PAXLOVID N=1578 n/N_w (%)	Placebo N=1581 n/N_w (%)
Bilirubin ≥2X ULN and ALP ≥2X ULN (right upper)	0/984 (0)	0/996 (0)	0/515 (0)	0/506 (0)	0/1499 (0)	0/1502 (0)
Bilirubin ≥2X ULN and ALP <2X ULN (left upper)	2/984 (0.2)	0/996 (0)	1/515 (0.2)	3/506 (0.6)	3/1499 (0.2)	3/1502 (0.2)

	EPIC-HR		EPIC-SR		Pooled	
Quadrant	PAXLOVID N=1038 n/N_w (%)	Placebo N=1053 n/N_w (%)	PAXLOVID N=540 n/N_w (%)	Placebo N=528 n/N_w (%)	PAXLOVID N=1578 n/N_w (%)	Placebo N=1581 n/N_w (%)
Bilirubin <2X ULN and ALP ≥2X ULN (right lower)	1/984 (0.1)	4/996 (0.4)	1/515 (0.2)	0/506 (0)	2/1499 (0.1)	4/1502 (0.3)
Total	3/984 (0.3)	4/996 (0.4)	2/515 (0.4)	3/506 (0.6)	5/1499 (0.3)	7/1502 (0.5)

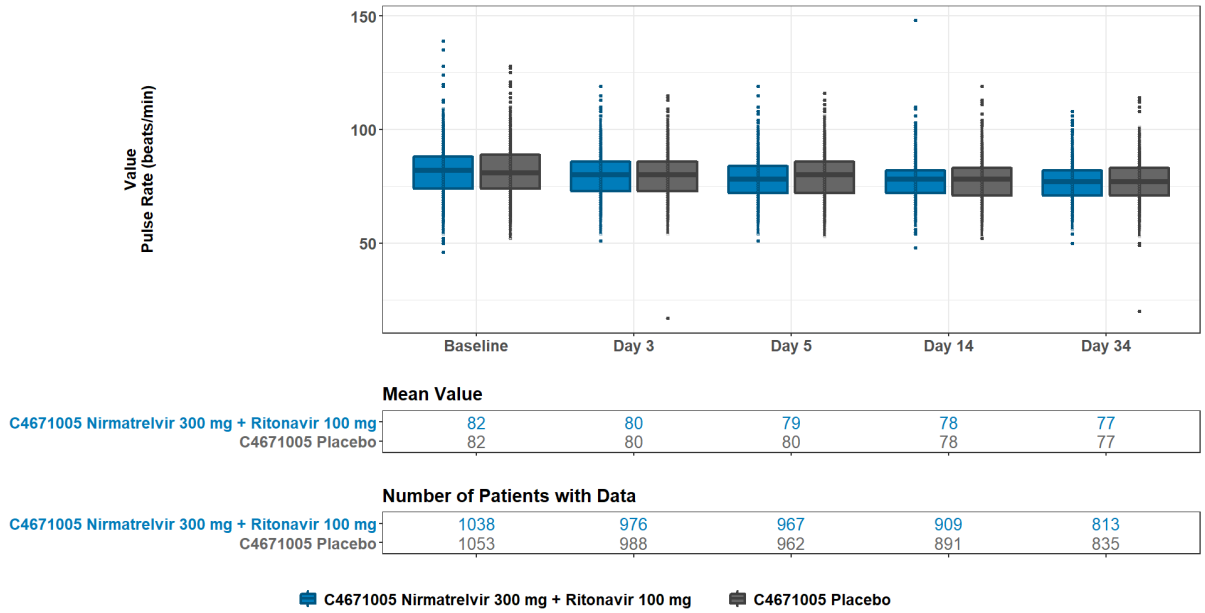
Source: adlb.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

17.7. Vital Sign Assessment, EPIC-HR and EPIC-SR

An overview of vital sign assessment was provided in Section 7.6.1.8. Figure 65, Figure 66, and Figure 67 describe pulse, respiration rate, and body temperature in EPIC-HR and EPIC-SR.

Figure 65. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

EPIC-HR



Mean Value

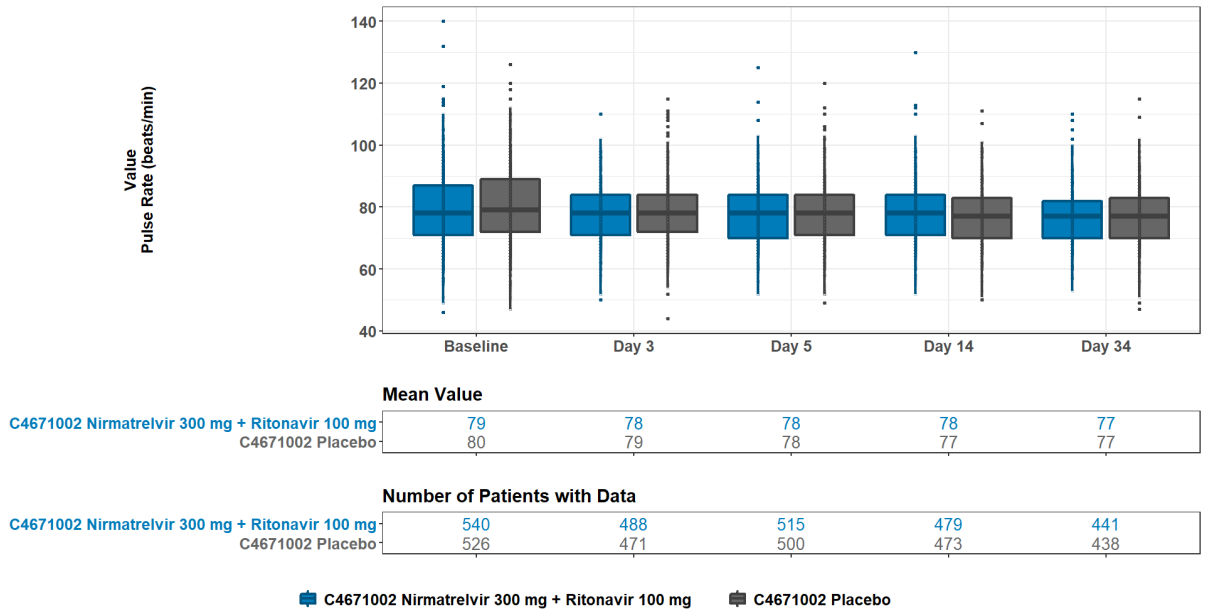
	Baseline	Day 3	Day 5	Day 14	Day 34
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	82	80	79	78	77
C4671005 Placebo	82	80	80	78	77

Number of Patients with Data

	Baseline	Day 3	Day 5	Day 14	Day 34
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	1038	976	967	909	813
C4671005 Placebo	1053	988	962	891	835

C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671005 Placebo

EPIC-SR



Mean Value

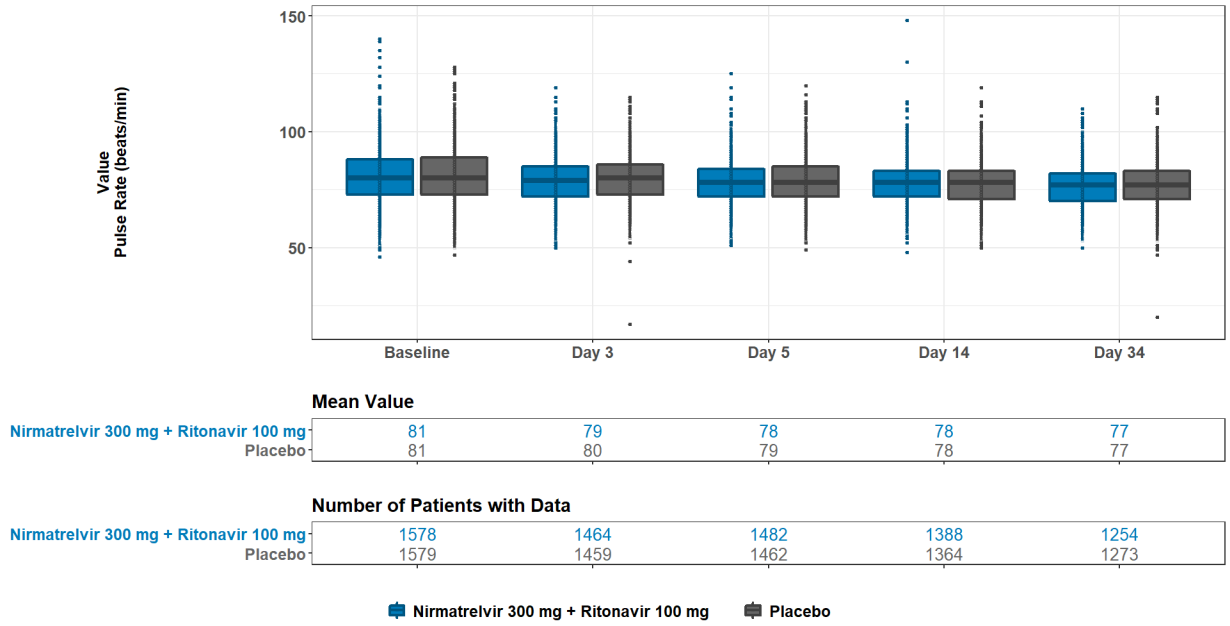
	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	79	78	78	78	77
C4671002 Placebo	80	79	78	77	77

Number of Patients with Data

	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	540	488	515	479	441
C4671002 Placebo	526	471	500	473	438

C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671002 Placebo

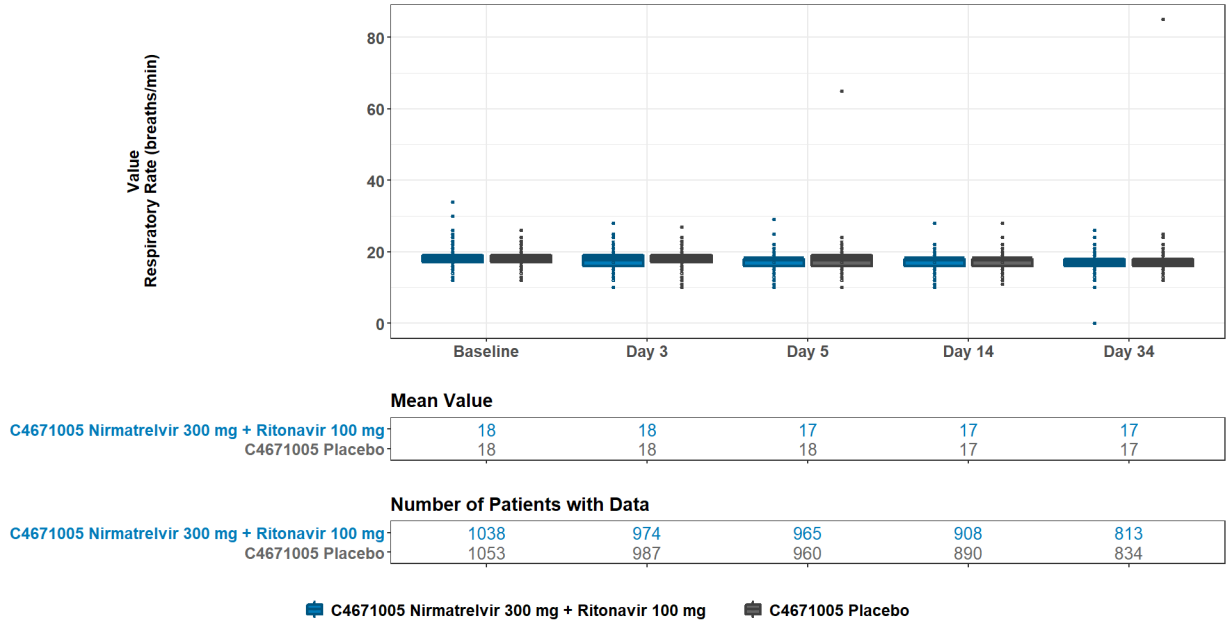
EPIC-HR and EPIC-SR



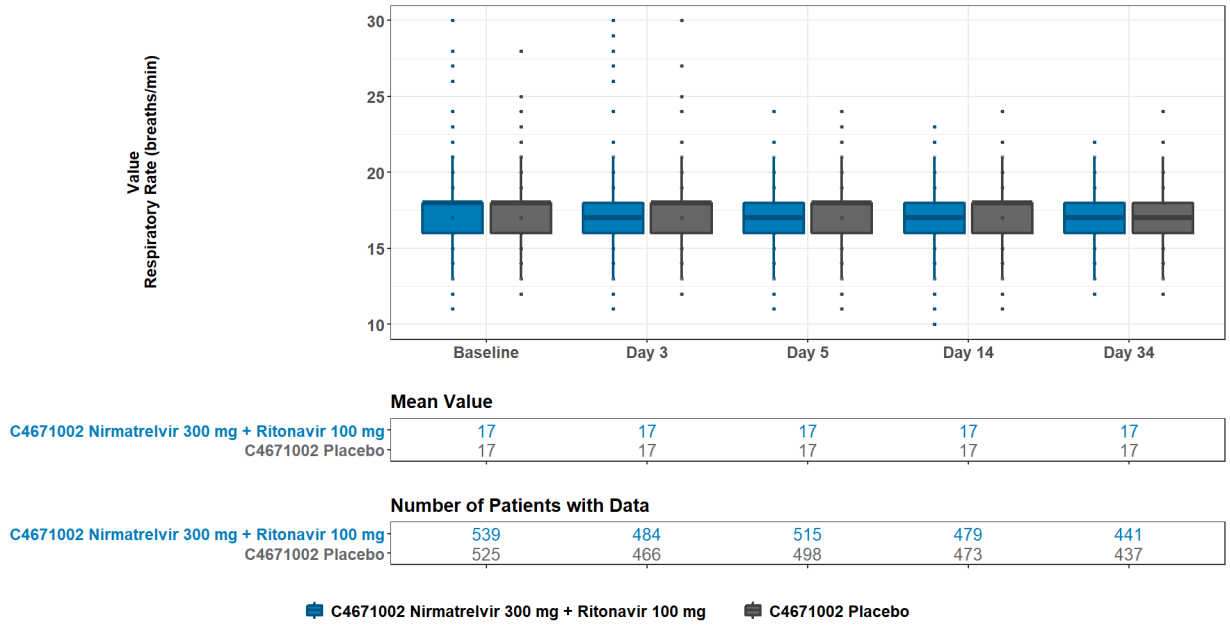
Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

Figure 66. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

EPIC-HR



EPIC-SR



Mean Value

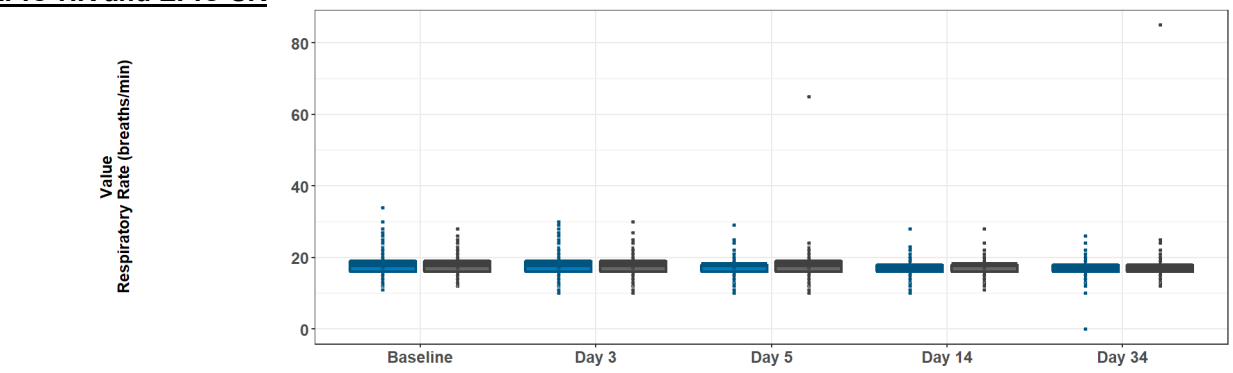
	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	17	17	17	17	17
C4671002 Placebo	17	17	17	17	17

Number of Patients with Data

	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	539	484	515	479	441
C4671002 Placebo	525	466	498	473	437

C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671002 Placebo

EPIC-HR and EPIC-SR



Mean Value

	Baseline	Day 3	Day 5	Day 14	Day 34
Nirmatrelvir 300 mg + Ritonavir 100 mg	18	17	17	17	17
Placebo	18	18	18	17	17

Number of Patients with Data

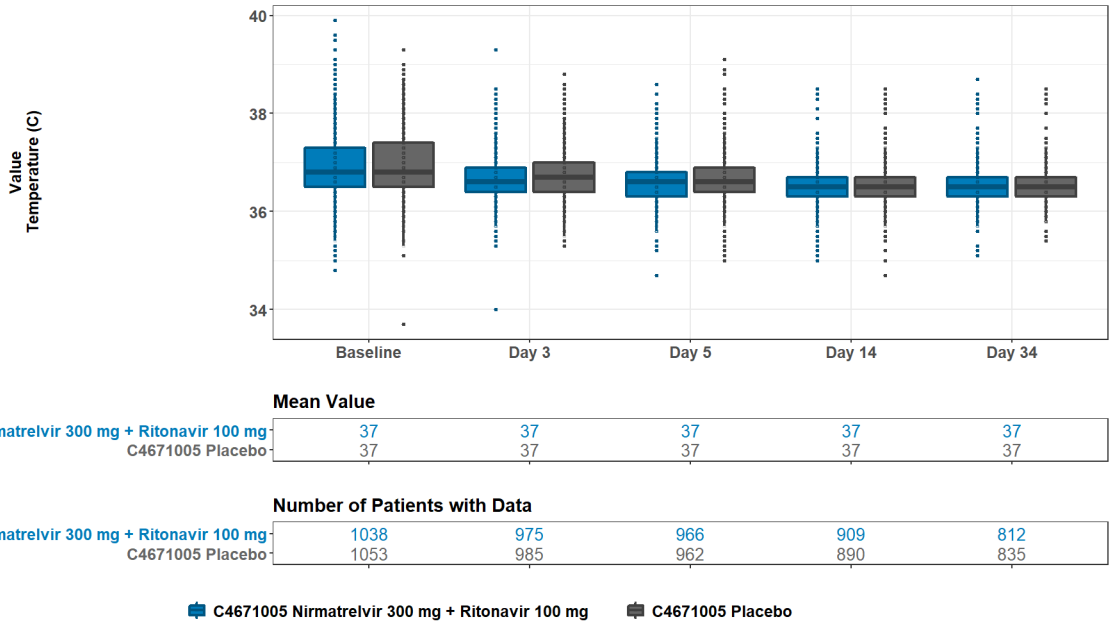
	Baseline	Day 3	Day 5	Day 14	Day 34
Nirmatrelvir 300 mg + Ritonavir 100 mg	1577	1458	1480	1387	1254
Placebo	1578	1453	1458	1363	1271

Nirmatrelvir 300 mg + Ritonavir 100 mg Placebo

Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-SR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-HR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

Figure 67. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, Safety Population, EPIC-HR and EPIC-SR

EPIC-HR



Mean Value

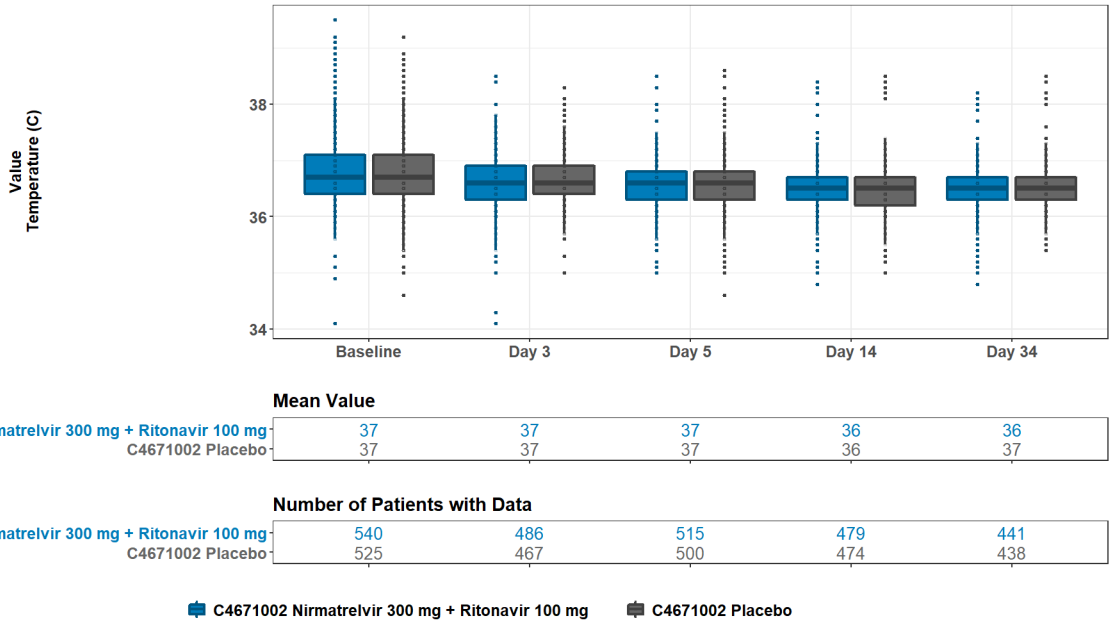
	Baseline	Day 3	Day 5	Day 14	Day 34
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	37	37	37	37	37
C4671005 Placebo	37	37	37	37	37

Number of Patients with Data

	Baseline	Day 3	Day 5	Day 14	Day 34
C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg	1038	975	966	909	812
C4671005 Placebo	1053	985	962	890	835

C4671005 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671005 Placebo

EPIC-SR



Mean Value

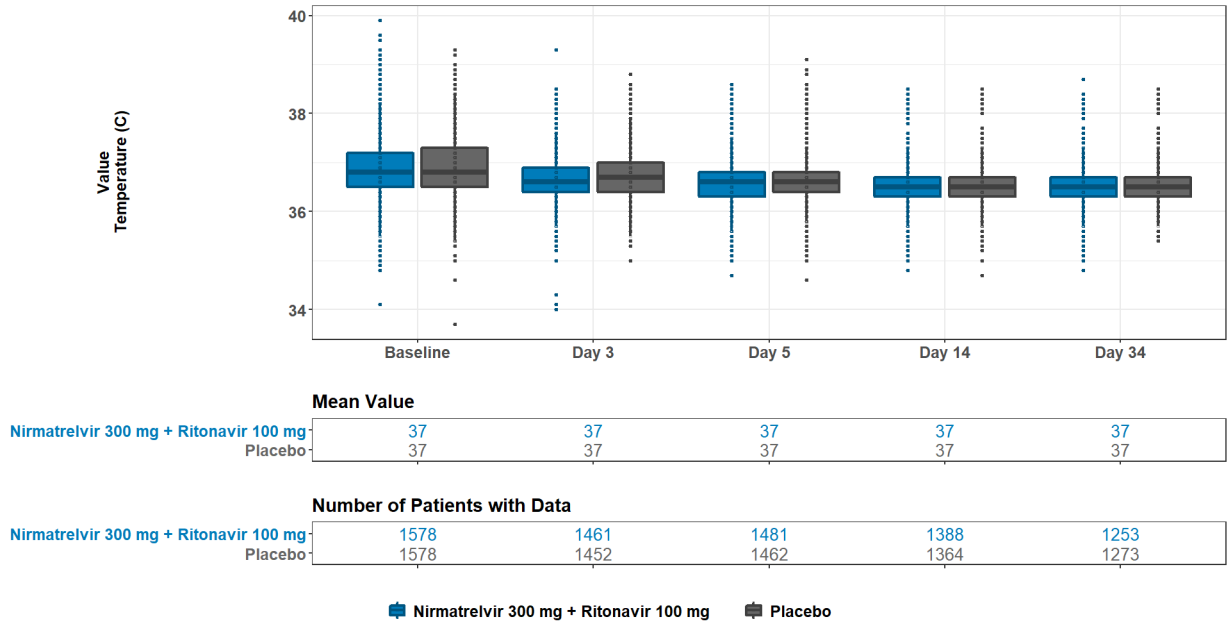
	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	37	37	37	36	36
C4671002 Placebo	37	37	37	36	37

Number of Patients with Data

	Baseline	Day 3	Day 5	Day 14	Day 34
C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg	540	486	515	479	441
C4671002 Placebo	525	467	500	474	438

C4671002 Nirmatrelvir 300 mg + Ritonavir 100 mg C4671002 Placebo

EPIC-HR and EPIC-SR



Source: advs.xpt; Software: R.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Note: Extreme outlier values are excluded.
Note: C4671002 = EPIC-SR, C4671005 = EPIC-HR.

17.8. Demographic Subgroup Analysis, EPIC-HR and EPIC-SR

An overview of adverse events by demographic subgroups in EPIC-HR and EPIC-SR was presented in Section 7.6.1.9. Table 157 and Table 158 describe adverse events by demographic subgroups in EPIC-HR and EPIC-SR.

Table 157. Overview of Adverse Events by Demographic Subgroup, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_S (%)	Placebo N=1053 n/N_S (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_S (%)	Placebo N=528 n/N_S (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_S (%)	Placebo N=1581 n/N_S (%)	Risk Difference (%) (95% CI)
Sex, n (%)									
Female	125/522 (23.9)	131/515 (25.4)	-1.5 (-6.7, 3.8)	56/275 (20.4)	75/284 (26.4)	-6.0 (-13.0, 1.0)	181/797 (22.7)	206/799 (25.8)	-3.1 (-7.3, 1.1)
Male	103/516 (20.0)	125/538 (23.2)	-3.3 (-8.2, 1.7)	70/265 (26.4)	51/244 (20.9)	5.5 (-1.8, 12.9)	173/781 (22.2)	176/782 (22.5)	-0.4 (-4.5, 3.8)
Age group, years, n (%)									
18 to 44	93/534 (17.4)	89/499 (17.8)	-0.4 (-5.1, 4.2)	65/328 (19.8)	65/310 (21.0)	-1.2 (-7.4, 5.1)	158/862 (18.3)	154/809 (19.0)	-0.7 (-4.4, 3.0)
45 to 59	62/306 (20.3)	82/316 (25.9)	-5.7 (-12.3, 0.9)	39/157 (24.8)	45/169 (26.6)	-1.8 (-11.3, 7.7)	101/463 (21.8)	127/485 (26.2)	-4.4 (-9.8, 1.1)
60 to 64	19/69 (27.5)	36/104 (34.6)	-7.1 (-21.0, 6.9)	6/19 (31.6)	6/24 (25.0)	6.6 (-20.6, 33.7)	25/88 (28.4)	42/128 (32.8)	-4.4 (-16.9, 8.0)
65 to 74	35/96 (36.5)	35/103 (34.0)	2.5 (-10.8, 15.8)	13/30 (43.3)	6/15 (40.0)	3.3 (-27.1, 33.8)	48/126 (38.1)	41/118 (34.7)	3.3 (-8.7, 15.4)
≥75	19/33 (57.6)	14/31 (45.2)	12.4 (-11.9, 36.7)	3/6 (50.0)	4/10 (40.0)	10.0 (-40.2, 60.2)	22/39 (56.4)	18/41 (43.9)	12.5 (-9.2, 34.3)
Age group ≥65, years, n (%)									
≥65	54/129 (41.9)	49/134 (36.6)	5.3 (-6.5, 17.1)	16/36 (44.4)	10/25 (40.0)	4.4 (-20.7, 29.6)	70/165 (42.4)	59/159 (37.1)	5.3 (-5.3, 16.0)
Race, n (%)									
American Indian or Alaska Native	18/95 (18.9)	19/94 (20.2)	-1.3 (-12.6, 10.0)	2/23 (8.7)	9/18 (50.0)	-41.3 (-67.1, -15.5)	20/118 (16.9)	28/112 (25.0)	-8.1 (-18.5, 2.4)
Asian	43/153 (28.1)	30/156 (19.2)	8.9 (-0.6, 18.3)	14/67 (20.9)	14/70 (20.0)	0.9 (-12.6, 14.4)	57/220 (25.9)	44/226 (19.5)	6.4 (-1.3, 14.2)
Black or African American	8/52 (15.4)	8/35 (22.9)	-7.5 (-24.5, 9.5)	4/19 (21.1)	4/18 (22.2)	-1.2 (-27.7, 25.4)	12/71 (16.9)	12/53 (22.6)	-5.7 (-20.0, 8.5)
Multiple	0/1 (0)	0/2 (0)	0 (0, 0)	0/0 (NA)	0/0 (NA)	NA	0/1 (0)	0/2 (0)	0 (0, 0)
Unknown	0/1 (0)	1/1 (100)	-100.0 (-100.0, -100.0)	1/1 (100)	1/2 (50.0)	50.0 (-19.3, 119.3)	1/2 (50.0)	2/3 (66.7)	-16.7 (-104.1, 70.8)
White	158/728 (21.7)	195/756 (25.8)	-4.1 (-8.4, 0.2)	102/425 (24.0)	95/413 (23.0)	1.0 (-4.7, 6.7)	260/1153 (22.5)	290/1169 (24.8)	-2.3 (-5.7, 1.2)
Missing	1/8 (12.5)	3/9 (33.3)	-20.8 -59.2, 17.6)	3/5 (60.0)	3/7 (42.9)	17.1 (-39.3, 73.6)	4/13 (30.8)	6/16 (37.5)	-6.7 (-41.3, 27.8)

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_s (%)	Placebo N=1053 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_s (%)	Placebo N=528 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_s (%)	Placebo N=1581 n/N_s (%)	Risk Difference (%) (95% CI)
Ethnicity, n (%)									
Hispanic or Latino	51/425 (12.0)	71/439 (16.2)	-4.2 (-8.8, 0.5)	28/233 (12.0)	43/224 (19.2)	-7.2 (-13.8, -0.5)	79/658 (12.0)	114/663 (17.2)	-5.2 (-9.0, -1.4)
Not Hispanic or Latino	174/608 (28.6)	182/607 (30.0)	-1.4 (-6.5, 3.8)	96/304 (31.6)	81/299 (27.1)	4.5 (-2.8, 11.7)	270/912 (29.6)	263/906 (29.0)	0.6 (-3.6, 4.8)
Not Reported	3/5 (60.0)	3/7 (42.9)	17.1 (-39.3, 73.6)	2/3 (66.7)	2/5 (40.0)	26.7 (-41.8, 95.1)	5/8 (62.5)	5/12 (41.7)	20.8 (-22.8, 64.5)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 158. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_s (%)	Placebo N=1053 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_s (%)	Placebo N=528 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_s (%)	Placebo N=1581 n/N_s (%)	Risk Difference (%) (95% CI)
Sex, n (%)									
Female	8/522 (1.5)	29/515 (5.6)	-4.1 (-6.4, -1.8)	3/275 (1.1)	7/284 (2.5)	-1.4 (-3.6, 0.8)	11/797 (1.4)	36/799 (4.5)	-3.1 (-4.8, -1.5)
Male	10/516 (1.9)	42/538 (7.8)	-5.9 (-8.4, -3.3)	5/265 (1.9)	4/244 (1.6)	0.2 (-2.0, 2.5)	15/781 (1.9)	46/782 (5.9)	-4.0 (-5.9, -2.1)
Age group, years, n (%)									
18 to 44	3/534 (0.6)	13/499 (2.6)	-2.0 (-3.6, -0.5)	1/328 (0.3)	5/310 (1.6)	-1.3 (-2.8, 0.2)	4/862 (0.5)	18/809 (2.2)	-1.8 (-2.9, -0.6)
45 to 59	10/306 (3.3)	27/316 (8.5)	-5.3 (-8.9, -1.6)	5/157 (3.2)	3/169 (1.8)	1.4 (-2.0, 4.8)	15/463 (3.2)	30/485 (6.2)	-2.9 (-5.6, -0.3)
60 to 64	1/69 (1.4)	10/104 (9.6)	-8.2 (-14.5, -1.8)	1/19 (5.3)	0/24 (0)	5.3 (-4.8, 15.3)	2/88 (2.3)	10/128 (7.8)	-5.5 (-11.1, 0.1)
65 to 74	3/96 (3.1)	15/103 (14.6)	-11.4 (-19.1, -3.8)	1/30 (3.3)	2/15 (13.3)	-10.0 (-28.4, 8.4)	4/126 (3.2)	17/118 (14.4)	-11.2 (-18.3, -4.2)
≥75	1/33 (3.0)	6/31 (19.4)	-16.3 (-31.4, -1.2)	0/6 (0)	1/10 (10.0)	-10.0 (-28.6, 8.6)	1/39 (2.6)	7/41 (17.1)	-14.5 (-27.0, -2.0)
Age group ≥65, years, n (%)									
≥65	4/129 (3.1)	21/134 (15.7)	-12.6 (-19.4, -5.7)	1/36 (2.8)	3/25 (12.0)	-9.2 (-23.0, 4.6)	5/165 (3.0)	24/159 (15.1)	-12.1 (-18.2, -5.9)
Race, n (%)									
American Indian or Alaska Native	1/95 (1.1)	5/94 (5.3)	-4.3 (-9.2, 0.7)	0/23 (0)	2/18 (11.1)	-11.1 (-25.6, 3.4)	1/118 (0.8)	7/112 (6.2)	-5.4 (-10.2, -0.6)
Asian	2/153 (1.3)	7/156 (4.5)	-3.2 (-6.9, 0.5)	1/67 (1.5)	0/70 (0)	1.5 (-1.4, 4.4)	3/220 (1.4)	7/226 (3.1)	-1.7 (-4.5, 1.0)
Black or African American	1/52 (1.9)	2/35 (5.7)	-3.8 (-12.3, 4.8)	0/19 (0)	0/18 (0)	0 (0, 0)	1/71 (1.4)	2/53 (3.8)	-2.4 (-8.2, 3.5)
Multiple	0/1 (0)	0/2 (0)	0 (0, 0)	0/0 (NA)	0/0 (NA)	NA	0/1 (0)	0/2 (0)	0 (0, 0)
Unknown	0/1 (0)	0/1 (0)	0 (0, 0)	0/1 (0)	0/2 (0)	0 (0, 0)	0/2 (0)	0/3 (0)	0 (0, 0)
White	14/728 (1.9)	56/756 (7.4)	-5.5 (-7.6, -3.4)	7/425 (1.6)	9/413 (2.2)	-0.5 (-2.4, 1.3)	21/1153 (1.8)	65/1169 (5.6)	-3.7 (-5.3, -2.2)
Missing	0/8 (0)	1/9 (11.1)	-11.1 (-31.6, 9.4)	0/5 (0)	0/7 (0)	0 (0, 0)	0/13 (0)	1/16 (6.2)	-6.2 (-18.1, 5.6)
Ethnicity, n (%)									

	EPIC-HR			EPIC-SR			Pooled		
Characteristic	PAXLOVID N=1038 n/N_s (%)	Placebo N=1053 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/N_s (%)	Placebo N=528 n/N_s (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/N_s (%)	Placebo N=1581 n/N_s (%)	Risk Difference (%) (95% CI)
Hispanic or Latino	3/425 (0.7)	13/439 (3.0)	-2.3 (-4.0, -0.5)	1/233 (0.4)	5/224 (2.2)	-1.8 (-3.9, 0.3)	4/658 (0.6)	18/663 (2.7)	-2.1 (-3.5, -0.7)
Not Hispanic or Latino	15/608 (2.5)	57/607 (9.4)	-6.9 (-9.6, -4.3)	7/304 (2.3)	6/299 (2.0)	0.3 (-2.0, 2.6)	22/912 (2.4)	63/906 (7.0)	-4.5 (-6.5, -2.6)
Not Reported	0/5 (0)	1/7 (14.3)	-14.3 (-40.2, 11.6)	0/3 (0)	0/5 (0)	0 (0, 0)	0/8 (0)	1/12 (8.3)	-8.3 (-24.0, 7.3)

Source: adae.xpt; Software: R.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

17.9. Adverse Event Assessment, EPIC-PEP

Overviews of adverse events in EPIC-PEP were provided in Sections 7.6.2.3, 7.6.2.4, and 7.6.2.5. Assessment of adverse using FMQs to evaluate SAEs (Table 159), AEs leading to treatment discontinuation (Table 160), and patients with adverse events (Table 161 and Table 162) were similar to the respective assessments using preferred terms.

Reference ID: 5179402

Table 159. Patients With Serious Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Infections and infestations (SOC)						
Bacterial Infection	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Viral Infection	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 160. Patients With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Gastrointestinal disorders (SOC)						
Nausea	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
Dyspepsia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Hepatobiliary disorders (SOC)						
Hepatic Injury	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)
Infections and infestations (SOC)						
Viral Infection	0	1 (0.1)	2 (0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.5, 0.3)	-0.1 (-0.3, 0.1)

System Organ Class FMQ (Narrow)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Nervous system disorders (SOC)						
Headache	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dysgeusia	2 (0.2)	2 (0.2)	1 (0.1)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	-0.0 (-0.4, 0.4)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Vascular disorders (SOC)						
Hemorrhage	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 161. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow), Safety Population, EPIC-PEP[2]

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)						
Anemia	5 (0.5)	3 (0.3)	3 (0.3)	0.2 (-0.4, 0.8)	-0.0 (-0.5, 0.5)	0.2 (-0.4, 0.8)
Thrombocytopenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Leukopenia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Cardiac disorders (SOC)						
Arrhythmia	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Systemic Hypertension	2 (0.2)	3 (0.3)	1 (0.1)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)	-0.1 (-0.6, 0.4)
Endocrine disorders (SOC)						
Hyperglycemia	5 (0.5)	2 (0.2)	4 (0.4)	0.1 (-0.5, 0.8)	-0.2 (-0.8, 0.3)	0.3 (-0.2, 0.9)

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Gastrointestinal disorders (SOC)						
Diarrhea	23 (2.5)	22 (2.4)	15 (1.7)	0.9 (-0.5, 2.2)	0.7 (-0.6, 2.0)	0.1 (-1.3, 1.5)
Vomiting	7 (0.8)	3 (0.3)	3 (0.3)	0.4 (-0.2, 1.1)	-0.0 (-0.5, 0.5)	0.4 (-0.2, 1.1)
Nausea	16 (1.8)	12 (1.3)	14 (1.6)	0.2 (-1.0, 1.4)	-0.2 (-1.3, 0.9)	0.4 (-0.7, 1.6)
Dry Mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Dyspepsia	3 (0.3)	5 (0.5)	2 (0.2)	0.1 (-0.4, 0.6)	0.3 (-0.2, 0.9)	-0.2 (-0.8, 0.4)
Abdominal Pain	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
General disorders and administration site conditions (SOC)						
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Pyrexia	1 (0.1)	3 (0.3)	6 (0.7)	-0.6 (-1.1, 0.0)	-0.3 (-1.0, 0.3)	-0.2 (-0.6, 0.2)
Fatigue	13 (1.4)	10 (1.1)	18 (2.0)	-0.6 (-1.8, 0.6)	-0.9 (-2.0, 0.2)	0.3 (-0.7, 1.4)
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Hepatic Injury	3 (0.3)	7 (0.8)	12 (1.3)	-1.0 (-1.8, -0.2)*	-0.6 (-1.5, 0.4)	-0.4 (-1.1, 0.2)
Infections and infestations (SOC)						
Nasopharyngitis	16 (1.8)	11 (1.2)	7 (0.8)	1.0 (-0.1, 2.0)	0.4 (-0.5, 1.3)	0.5 (-0.6, 1.7)
Bacterial Infection	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Pneumonia	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Viral Infection	35 (3.8)	32 (3.5)	45 (5.0)	-1.2 (-3.1, 0.7)	-1.5 (-3.4, 0.4)	0.3 (-1.4, 2.1)
Metabolism and nutrition disorders (SOC)						
Lipid Disorder	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	2 (0.2)	0	0	0.2 (-0.1, 0.5)	0 (0, 0)	0.2 (-0.1, 0.5)
Back Pain	1 (0.1)	2 (0.2)	1 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)	-0.1 (-0.5, 0.3)
Myalgia	3 (0.3)	2 (0.2)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.8 (-1.5, -0.1)*	0.1 (-0.4, 0.6)
Nervous system disorders (SOC)						
Dysgeusia	54 (5.9)	63 (6.9)	6 (0.7)	5.3 (3.6, 6.9)*	6.2 (4.5, 8.0)*	-1.0 (-3.2, 1.3)
Somnolence	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Syncope	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)
Psychiatric disorders (SOC)						
Study Agent Abuse Potential	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Arthritis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Insomnia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

System Organ Class FMQ[4] (Narrow)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Renal and urinary disorders (SOC)						
Renal and Urinary Tract Infection	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Acute Kidney Injury	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Reproductive system and breast disorders (SOC)						
Abnormal Uterine Bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Excessive Menstrual Bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)						
Dyspnea	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Bronchospasm	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Cough	10 (1.1)	2 (0.2)	12 (1.3)	-0.2 (-1.3, 0.8)	-1.1 (-1.9, -0.3)*	0.9 (0.1, 1.6)*
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Erythema	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Vascular disorders (SOC)						
Hemorrhage	3 (0.3)	3 (0.3)	0	0.3 (-0.0, 0.7)	0.3 (-0.0, 0.7)	-0.0 (-0.5, 0.5)

Source: adae.xpt; Software: R.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1]Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2]Duration of treatment is 5 or 10 days.
[3]Difference is shown between PAXLOVID vs placebo
[4]Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 162. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query (Broad), Safety Population, EPIC-PEP[2]

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Blood and lymphatic system disorders (SOC)						
Anemia	5 (0.5)	3 (0.3)	3 (0.3)	0.2 (-0.4, 0.8)	-0.0 (-0.5, 0.5)	0.2 (-0.4, 0.8)
Thrombocytopenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Leukopenia	2 (0.2)	3 (0.3)	2 (0.2)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)	-0.1 (-0.6, 0.4)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Cardiac disorders (SOC)						
Systemic hypertension	2 (0.2)	3 (0.3)	1 (0.1)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)	-0.1 (-0.6, 0.4)
Arrhythmia	3 (0.3)	2 (0.2)	2 (0.2)	0.1 (-0.4, 0.6)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)
Heart failure	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Acute coronary syndrome	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Ear and labyrinth disorders (SOC)						
Vertigo	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Endocrine disorders (SOC)						
Hyperglycemia	5 (0.5)	2 (0.2)	5 (0.6)	-0.0 (-0.7, 0.7)	-0.3 (-0.9, 0.2)	0.3 (-0.2, 0.9)
Diabetic ketoacidosis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Hypoglycemia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Gastrointestinal disorders (SOC)						
Diarrhea	24 (2.6)	23 (2.5)	16 (1.8)	0.8 (-0.5, 2.2)	0.7 (-0.6, 2.1)	0.1 (-1.3, 1.6)
Vomiting	17 (1.9)	16 (1.8)	15 (1.7)	0.2 (-1.0, 1.4)	0.1 (-1.1, 1.3)	0.1 (-1.1, 1.3)
Dry mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Nausea	16 (1.8)	15 (1.6)	15 (1.7)	0.1 (-1.1, 1.3)	-0.0 (-1.2, 1.2)	0.1 (-1.1, 1.3)
Abdominal pain	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
Dyspepsia	5 (0.5)	7 (0.8)	6 (0.7)	-0.1 (-0.8, 0.6)	0.1 (-0.7, 0.9)	-0.2 (-1.0, 0.5)
General disorders and administration site conditions (SOC)						
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Fall	2 (0.2)	2 (0.2)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)
Pyrexia	5 (0.5)	3 (0.3)	8 (0.9)	-0.3 (-1.1, 0.4)	-0.6 (-1.3, 0.2)	0.2 (-0.4, 0.8)
Fatigue	14 (1.5)	10 (1.1)	18 (2.0)	-0.5 (-1.7, 0.7)	-0.9 (-2.0, 0.2)	0.4 (-0.6, 1.5)
Hepatobiliary disorders (SOC)						
Cholecystitis	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Hepatic failure	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Hepatic injury	4 (0.4)	8 (0.9)	14 (1.6)	-1.1 (-2.0, -0.2)*	-0.7 (-1.7, 0.3)	-0.4 (-1.2, 0.3)
Immune system disorders (SOC)						
Hypersensitivity	1 (0.1)	3 (0.3)	2 (0.2)	-0.1 (-0.5, 0.3)	0.1 (-0.4, 0.6)	-0.2 (-0.6, 0.2)
Infections and infestations (SOC)						
Nasopharyngitis	16 (1.8)	11 (1.2)	7 (0.8)	1.0 (-0.1, 2.0)	0.4 (-0.5, 1.3)	0.5 (-0.6, 1.7)
Bacterial infection	2 (0.2)	1 (0.1)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)
Pneumonia	3 (0.3)	4 (0.4)	8 (0.9)	-0.6 (-1.3, 0.2)	-0.5 (-1.2, 0.3)	-0.1 (-0.7, 0.5)
Viral infection	56 (6.1)	51 (5.6)	67 (7.5)	-1.3 (-3.6, 1.0)	-1.9 (-4.1, 0.4)	0.5 (-1.6, 2.7)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Metabolism and nutrition disorders (SOC)						
Lipid disorder	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Musculoskeletal and connective tissue disorders (SOC)						
Fracture	2 (0.2)	0	0	0.2 (-0.1, 0.5)	0 (0, 0)	0.2 (-0.1, 0.5)
Arthralgia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Back Pain	1 (0.1)	2 (0.2)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.3)
Rhabdomyolysis	12 (1.3)	15 (1.6)	13 (1.4)	-0.1 (-1.2, 0.9)	0.2 (-0.9, 1.3)	-0.3 (-1.4, 0.8)
Myalgia	3 (0.3)	3 (0.3)	9 (1.0)	-0.7 (-1.4, 0.1)	-0.7 (-1.4, 0.1)	-0.0 (-0.5, 0.5)
Nervous system disorders (SOC)						
Dysgeusia	55 (6.0)	63 (6.9)	7 (0.8)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Somnolence	3 (0.3)	3 (0.3)	1 (0.1)	0.2 (-0.2, 0.6)	0.2 (-0.2, 0.6)	-0.0 (-0.5, 0.5)
Confusional state	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Syncope	2 (0.2)	2 (0.2)	2 (0.2)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)	-0.0 (-0.4, 0.4)
Headache	15 (1.6)	17 (1.9)	29 (3.2)	-1.6 (-3.0, -0.2)*	-1.4 (-2.8, 0.1)	-0.2 (-1.4, 1.0)
Psychiatric disorders (SOC)						
Anxiety	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Study agent abuse potential	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Depression	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Insomnia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Self-harm	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Arthritis	0	0	2 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Renal and urinary disorders (SOC)						
Acute kidney injury	10 (1.1)	7 (0.8)	8 (0.9)	0.2 (-0.7, 1.1)	-0.1 (-1.0, 0.7)	0.3 (-0.6, 1.2)
Urinary retention	0	1 (0.1)	1 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Renal and urinary tract infection	1 (0.1)	1 (0.1)	2 (0.2)	-0.1 (-0.5, 0.3)	-0.1 (-0.5, 0.3)	-0.0 (-0.3, 0.3)
Reproductive system and breast disorders (SOC)						
Abnormal uterine bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Excessive menstrual bleeding	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

System Organ Class FMQ (Broad)[4]	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs. PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Respiratory, thoracic and mediastinal disorders (SOC)						
Bronchospasm	4 (0.4)	3 (0.3)	3 (0.3)	0.1 (-0.5, 0.7)	-0.0 (-0.5, 0.5)	0.1 (-0.5, 0.7)
Dyspnea	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Respiratory failure	4 (0.4)	2 (0.2)	3 (0.3)	0.1 (-0.5, 0.7)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.7)
Pneumonitis	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Cough	10 (1.1)	2 (0.2)	13 (1.4)	-0.4 (-1.4, 0.7)	-1.2 (-2.1, -0.4)*	0.9 (0.1, 1.6)*
Skin and subcutaneous tissue disorders (SOC)						
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Urticaria	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Erythema	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Vascular disorders (SOC)						
Hemorrhage	3 (0.3)	3 (0.3)	0	0.3 (-0.0, 0.7)	0.3 (-0.0, 0.7)	-0.0 (-0.5, 0.5)

Source: adae.xpt; Software: R.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo
[4.] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Broad) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 163 includes the AEs considered by the investigator to be related to study drug in EPIC-PEP. These AEs were previously discussed in Section 7.6.2.5.

Reference ID: 5179402

Table 163. Patients With Adverse Events Assessed by Investigator as Treatment-Related, Safety Population, Trial EPIC-PEP

Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Any treatment-related AE	86 (9.4)	107 (11.7)	49 (5.5)	4.0 (1.6, 6.4)*	6.3 (3.7, 8.9)*	-2.3 (-5.1, 0.5)
Dysgeusia	54 (5.9)	62 (6.8)	6 (0.7)	5.3 (3.6, 6.9)*	6.1 (4.4, 7.9)*	-0.9 (-3.1, 1.4)
Vomiting	6 (0.7)	0	1 (0.1)	0.5 (-0.0, 1.1)	-0.1 (-0.3, 0.1)	0.7 (0.1, 1.2)*
Diarrhea	11 (1.2)	14 (1.5)	7 (0.8)	0.4 (-0.5, 1.3)	0.8 (-0.2, 1.7)	-0.3 (-1.4, 0.7)
Oropharyngeal pain	2 (0.2)	1 (0.1)	0	0.2 (-0.1, 0.5)	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.5)
Blood fibrinogen decreased	3 (0.3)	1 (0.1)	1 (0.1)	0.2 (-0.2, 0.6)	-0.0 (-0.3, 0.3)	0.2 (-0.2, 0.6)
Blood calcium decreased	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dry mouth	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Dyspnea	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Fibrin D dimer increased	1 (0.1)	4 (0.4)	0	0.1 (-0.1, 0.3)	0.4 (0.0, 0.9)*	-0.3 (-0.8, 0.2)
Gastroesophageal reflux disease	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
International normalized ratio increased	1 (0.1)	1 (0.1)	0	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Pain	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Serum ferritin increased	1 (0.1)	0	0	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Dizziness	2 (0.2)	0	1 (0.1)	0.1 (-0.3, 0.5)	-0.1 (-0.3, 0.1)	0.2 (-0.1, 0.5)
Blood thyroid stimulating hormone increased	6 (0.7)	5 (0.5)	5 (0.6)	0.1 (-0.6, 0.8)	-0.0 (-0.7, 0.7)	0.1 (-0.6, 0.8)
Back pain	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Blood lactate dehydrogenase increased	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Dysuria	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Eosinophilia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Gastritis	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Gastroenteritis	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Hyperkalemia	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Rash	0	1 (0.1)	0	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Abdominal pain upper	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Cough	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Neutropenia	1 (0.1)	0	1 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Prothrombin time prolonged	1 (0.1)	1 (0.1)	1 (0.1)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.3)
Nausea	12 (1.3)	11 (1.2)	12 (1.3)	-0.0 (-1.1, 1.0)	-0.1 (-1.2, 0.9)	0.1 (-0.9, 1.1)
Chills	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Dyspepsia	0	3 (0.3)	1 (0.1)	-0.1 (-0.3, 0.1)	0.2 (-0.2, 0.6)	-0.3 (-0.7, 0.0)
Fatigue	0	2 (0.2)	1 (0.1)	-0.1 (-0.3, 0.1)	0.1 (-0.3, 0.5)	-0.2 (-0.5, 0.1)
Hepatic enzyme increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Platelet count increased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Pruritus	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)

Preferred Term	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Thrombocytopenia	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
White blood cell count decreased	0	0	1 (0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	0 (0, 0)
Aspartate aminotransferase increased	1 (0.1)	4 (0.4)	2 (0.2)	-0.1 (-0.5, 0.3)	0.2 (-0.3, 0.7)	-0.3 (-0.8, 0.2)
Nasal congestion	1 (0.1)	0	2 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.5, 0.1)	0.1 (-0.1, 0.3)
Activated partial thromboplastin time prolonged	7 (0.8)	8 (0.9)	8 (0.9)	-0.1 (-1.0, 0.7)	-0.0 (-0.9, 0.9)	-0.1 (-0.9, 0.7)
Pyrexia	0	0	2 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Alanine aminotransferase increased	1 (0.1)	2 (0.2)	3 (0.3)	-0.2 (-0.7, 0.2)	-0.1 (-0.6, 0.4)	-0.1 (-0.5, 0.3)
Myalgia	1 (0.1)	0	3 (0.3)	-0.2 (-0.7, 0.2)	-0.3 (-0.7, 0.0)	0.1 (-0.1, 0.3)
Headache	4 (0.4)	4 (0.4)	6 (0.7)	-0.2 (-0.9, 0.5)	-0.2 (-0.9, 0.5)	-0.0 (-0.6, 0.6)
Blood creatine phosphokinase increased	2 (0.2)	8 (0.9)	5 (0.6)	-0.3 (-0.9, 0.2)	0.3 (-0.5, 1.1)	-0.7 (-1.3, 0.0)
Asthenia	1 (0.1)	0	5 (0.6)	-0.4 (-1.0, 0.1)	-0.6 (-1.0, -0.1)*	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
Note: Duration of treatment is 5 or 10 days.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

17.10. Laboratory Findings, EPIC-PEP

Table 164, Table 165, and Table 166 describe laboratory outliers assessed by the Safety Standard & Figures Integrated Guide (August 2022). An overview was previously provided in Section 7.6.2.6.

Reference ID: 5179402

Table 164. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels[1], Safety Population, EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Sodium, low (mEq/L)						
Level 1 (<132)	11/893 (1.2)	9/891 (1.0)	5/882 (0.6)	0.7 (-0.2, 1.5)	0.4 (-0.4, 1.3)	0.2 (-0.8, 1.2)
Level 2 (<130)	3/893 (0.3)	2/891 (0.2)	2/882 (0.2)	0.1 (-0.4, 0.6)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.6)
Level 3 (<125)	2/893 (0.2)	1/891 (0.1)	1/882 (0.1)	0.1 (-0.3, 0.5)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)
Sodium, high (mEq/L)						
Level 1 (>150)	4/893 (0.4)	1/891 (0.1)	5/882 (0.6)	-0.1 (-0.8, 0.5)	-0.5 (-1.0, 0.1)	0.3 (-0.2, 0.8)
Level 2 (>155)	1/893 (0.1)	0/891 (0)	1/882 (0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)	0.1 (-0.1, 0.3)
Level 3 (>160)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Potassium, low (mEq/L)						
Level 1 (<3.6)	60/892 (6.7)	54/891 (6.1)	73/882 (8.3)	-1.6 (-4.0, 0.9)	-2.2 (-4.6, 0.2)	0.7 (-1.6, 2.9)
Level 2 (<3.4)	20/892 (2.2)	17/891 (1.9)	18/882 (2.0)	0.2 (-1.1, 1.5)	-0.1 (-1.4, 1.2)	0.3 (-1.0, 1.7)
Level 3 (<3)	0/892 (0)	1/891 (0.1)	0/882 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Potassium, high (mEq/L)						
Level 1 (>5.5)	21/892 (2.4)	32/891 (3.6)	37/882 (4.2)	-1.8 (-3.5, -0.2)	-0.6 (-2.4, 1.2)	-1.2 (-2.8, 0.3)
Level 2 (>6)	3/892 (0.3)	9/891 (1.0)	10/882 (1.1)	-0.8 (-1.6, -0.0)	-0.1 (-1.1, 0.8)	-0.7 (-1.4, 0.1)
Level 3 (>6.5)	0/892 (0)	2/891 (0.2)	4/882 (0.5)	-0.5 (-0.9, -0.0)	-0.2 (-0.8, 0.3)	-0.2 (-0.5, 0.1)
Chloride, low (mEq/L)						
Level 1 (<95)	56/893 (6.3)	45/891 (5.1)	32/882 (3.6)	2.6 (0.6, 4.7)	1.4 (-0.5, 3.3)	1.2 (-0.9, 3.4)
Level 2 (<88)	2/893 (0.2)	1/891 (0.1)	1/882 (0.1)	0.1 (-0.3, 0.5)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)
Level 3 (<80)	0/893 (0)	1/891 (0.1)	1/882 (0.1)	-0.1 (-0.3, 0.1)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.1)
Chloride, high (mEq/L)						
Level 1 (>108)	11/893 (1.2)	10/891 (1.1)	12/882 (1.4)	-0.1 (-1.2, 0.9)	-0.2 (-1.3, 0.8)	0.1 (-0.9, 1.1)
Level 2 (>112)	1/893 (0.1)	1/891 (0.1)	0/882 (0)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Level 3 (>115)	1/893 (0.1)	0/891 (0)	0/882 (0)	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)
Bicarbonate, low (mEq/L)						
Level 1 (<20)	182/893 (20.4)	175/891 (19.6)	205/882 (23.2)	-2.9 (-6.7, 1.0)	-3.6 (-7.4, 0.2)	0.7 (-3.0, 4.5)
Level 2 (<18)	54/893 (6.0)	40/891 (4.5)	57/882 (6.5)	-0.4 (-2.7, 1.8)	-2.0 (-4.1, 0.1)	1.6 (-0.5, 3.6)
Level 3 (<15)	4/893 (0.4)	1/891 (0.1)	6/882 (0.7)	-0.2 (-0.9, 0.5)	-0.6 (-1.2, 0.0)	0.3 (-0.2, 0.8)
Bicarbonate, high (mEq/L)						
Level 3 (>30)	10/893 (1.1)	11/891 (1.2)	15/882 (1.7)	-0.6 (-1.7, 0.5)	-0.5 (-1.6, 0.7)	-0.1 (-1.1, 0.9)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Glucose, low (mg/dL)						
Level 1 (<70)	112/893 (12.5)	127/891 (14.3)	122/882 (13.8)	-1.3 (-4.4, 1.9)	0.4 (-2.8, 3.7)	-1.7 (-4.9, 1.4)
Level 2 (<54)	18/893 (2.0)	24/891 (2.7)	30/882 (3.4)	-1.4 (-2.9, 0.1)	-0.7 (-2.3, 0.9)	-0.7 (-2.1, 0.7)
Level 3 (<40)	1/893 (0.1)	3/891 (0.3)	3/882 (0.3)	-0.2 (-0.7, 0.2)	-0.0 (-0.5, 0.5)	-0.2 (-0.7, 0.2)
Glucose, fasting, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Glucose, random, high (mg/dL)						
Level 2 (≥200)	52/893 (5.8)	43/891 (4.8)	42/882 (4.8)	1.1 (-1.0, 3.1)	0.1 (-1.9, 2.1)	1.0 (-1.1, 3.1)
Level 3 (>250)	31/893 (3.5)	25/891 (2.8)	23/882 (2.6)	0.9 (-0.7, 2.5)	0.2 (-1.3, 1.7)	0.7 (-1.0, 2.3)
Calcium, low (mg/dL)						
Level 1 (<8.4)	33/893 (3.7)	31/890 (3.5)	36/882 (4.1)	-0.4 (-2.2, 1.4)	-0.6 (-2.4, 1.2)	0.2 (-1.5, 1.9)
Level 2 (<8)	14/893 (1.6)	12/890 (1.3)	14/882 (1.6)	-0.0 (-1.2, 1.1)	-0.2 (-1.4, 0.9)	0.2 (-0.9, 1.3)
Level 3 (<7.5)	6/893 (0.7)	9/890 (1.0)	7/882 (0.8)	-0.1 (-0.9, 0.7)	0.2 (-0.7, 1.1)	-0.3 (-1.2, 0.5)
Calcium, high (mg/dL)						
Level 1 (>10.5)	24/893 (2.7)	17/890 (1.9)	12/882 (1.4)	1.3 (0.0, 2.6)	0.5 (-0.6, 1.7)	0.8 (-0.6, 2.2)
Level 2 (>11)	4/893 (0.4)	1/890 (0.1)	0/882 (0)	0.4 (0.0, 0.9)	0.1 (-0.1, 0.3)	0.3 (-0.2, 0.8)
Level 3 (>12)	0/893 (0)	0/890 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Magnesium, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)						
Level 1 (<6)	5/893 (0.6)	7/891 (0.8)	5/882 (0.6)	-0.0 (-0.7, 0.7)	0.2 (-0.5, 1.0)	-0.2 (-1.0, 0.5)
Level 2 (<5.4)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Level 3 (<5)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Albumin, low (g/dL)						
Level 1 (<3.1)	0/894 (0)	0/891 (0)	2/882 (0.2)	-0.2 (-0.5, 0.1)	-0.2 (-0.5, 0.1)	0 (0, 0)
Level 2 (<2.5)	0/894 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Level 3 (<2)	0/894 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
CPK, high (U/L)						
Level 1 (>3X ULN)	51/893 (5.7)	41/891 (4.6)	46/882 (5.2)	0.5 (-1.6, 2.6)	-0.6 (-2.6, 1.4)	1.1 (-0.9, 3.2)
Level 2 (>5X ULN)	24/893 (2.7)	19/891 (2.1)	21/882 (2.4)	0.3 (-1.2, 1.8)	-0.2 (-1.6, 1.1)	0.6 (-0.9, 2.0)
Level 3 (>10X ULN)	11/893 (1.2)	5/891 (0.6)	8/882 (0.9)	0.3 (-0.6, 1.3)	-0.3 (-1.1, 0.4)	0.7 (-0.2, 1.5)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Amylase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	46/893 (5.2)	26/891 (2.9)	41/882 (4.6)	0.5 (-1.5, 2.5)	-1.7 (-3.5, 0.0)	2.2 (0.4, 4.1)
Level 2 (>27)	17/893 (1.9)	12/891 (1.3)	9/882 (1.0)	0.9 (-0.2, 2.0)	0.3 (-0.7, 1.3)	0.6 (-0.6, 1.7)
Level 3 (>31)	8/893 (0.9)	5/891 (0.6)	6/882 (0.7)	0.2 (-0.6, 1.0)	-0.1 (-0.9, 0.6)	0.3 (-0.5, 1.1)
Creatinine, high (mg/dL)						
Level 1 (≥1.5X baseline)	57/885 (6.4)	45/872 (5.2)	44/869 (5.1)	1.4 (-0.8, 3.6)	0.1 (-2.0, 2.2)	1.3 (-0.9, 3.5)
Level 2 (≥2X baseline)	14/885 (1.6)	10/872 (1.1)	5/869 (0.6)	1.0 (0.0, 2.0)	0.6 (-0.3, 1.4)	0.4 (-0.6, 1.5)
Level 3 (≥3X baseline)	0/885 (0)	1/872 (0.1)	0/869 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
eGFR, low (ml/min/1.73 m^2)						
Level 1 (≥25% decrease)	93/885 (10.5)	78/872 (8.9)	68/868 (7.8)	2.7 (-0.0, 5.4)	1.1 (-1.5, 3.7)	1.6 (-1.2, 4.3)
Level 2 (≥50% decrease)	9/885 (1.0)	4/872 (0.5)	3/868 (0.3)	0.7 (-0.1, 1.4)	0.1 (-0.5, 0.7)	0.6 (-0.2, 1.4)
Level 3 (≥75% decrease)	0/885 (0)	0/872 (0)	0/868 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Source: adlb.xpt; Software: R
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Glucose values for hyperglycemia do not follow a nested format l ke the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 165. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels[1], Safety Population, Trial EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	4/893 (0.4)	7/891 (0.8)	11/882 (1.2)	-0.8 (-1.7, 0.1)	-0.5 (-1.4, 0.5)	-0.3 (-1.1, 0.4)
Level 2 (>2X ULN)	1/893 (0.1)	4/891 (0.4)	5/882 (0.6)	-0.5 (-1.0, 0.1)	-0.1 (-0.8, 0.5)	-0.3 (-0.8, 0.2)
Level 3 (>3X ULN)	0/893 (0)	0/891 (0)	0/882 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	12/893 (1.3)	8/891 (0.9)	8/882 (0.9)	0.4 (-0.5, 1.4)	-0.0 (-0.9, 0.9)	0.4 (-0.5, 1.4)
Level 2 (>5X ULN)	1/893 (0.1)	2/891 (0.2)	1/882 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.5)	-0.1 (-0.5, 0.3)
Level 3 (>10X ULN)	1/893 (0.1)	1/891 (0.1)	0/882 (0)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	-0.0 (-0.3, 0.3)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	3/893 (0.3)	7/891 (0.8)	2/882 (0.2)	0.1 (-0.4, 0.6)	0.6 (-0.1, 1.2)	-0.4 (-1.1, 0.2)
Level 2 (>5X ULN)	0/893 (0)	3/891 (0.3)	2/882 (0.2)	-0.2 (-0.5, 0.1)	0.1 (-0.4, 0.6)	-0.3 (-0.7, 0.0)
Level 3 (>10X ULN)	0/893 (0)	1/891 (0.1)	0/882 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	4/893 (0.4)	1/891 (0.1)	5/882 (0.6)	-0.1 (-0.8, 0.5)	-0.5 (-1.0, 0.1)	0.3 (-0.2, 0.8)
Level 2 (>2X ULN)	1/893 (0.1)	0/891 (0)	2/882 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.5, 0.1)	0.1 (-0.1, 0.3)
Level 3 (>3X ULN)	1/893 (0.1)	0/891 (0)	0/882 (0)	0.1 (-0.1, 0.3)	0 (0, 0)	0.1 (-0.1, 0.3)

Source: adlb.xpt; Software: R
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 166. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population[1], EPIC-PEP[2]

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
Complete Blood Count						
WBC, low (cells/uL)						
Level 1 (<3500)	45/871 (5.2)	50/863 (5.8)	54/859 (6.3)	-1.1 (-3.3, 1.1)	-0.5 (-2.7, 1.8)	-0.6 (-2.8, 1.5)
Level 2 (<3000)	26/871 (3.0)	23/863 (2.7)	28/859 (3.3)	-0.3 (-1.9, 1.4)	-0.6 (-2.2, 1.0)	0.3 (-1.2, 1.9)
Level 3 (<1000)	0/871 (0)	0/863 (0)	0/859 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
WBC, high (cells/uL)						
Level 1 (>10800)	79/871 (9.1)	75/863 (8.7)	61/859 (7.1)	2.0 (-0.6, 4.5)	1.6 (-1.0, 4.1)	0.4 (-2.3, 3.1)
Level 2 (>13000)	24/871 (2.8)	17/863 (2.0)	19/859 (2.2)	0.5 (-0.9, 2.0)	-0.2 (-1.6, 1.1)	0.8 (-0.6, 2.2)
Level 3 (>15000)	7/871 (0.8)	2/863 (0.2)	7/859 (0.8)	-0.0 (-0.9, 0.8)	-0.6 (-1.3, 0.1)	0.6 (-0.1, 1.2)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 dec. from BL)	78/707 (11.0)	67/668 (10.0)	74/662 (11.2)	-0.1 (-3.5, 3.2)	-1.1 (-4.5, 2.2)	1.0 (-2.2, 4.2)
Level 3 (>2 dec. from BL)	32/707 (4.5)	31/668 (4.6)	28/662 (4.2)	0.3 (-1.9, 2.5)	0.4 (-1.8, 2.6)	-0.1 (-2.3, 2.1)
Hemoglobin, high (g/dL)						
Level 2 (>2 inc. from BL)	7/707 (1.0)	16/668 (2.4)	13/662 (2.0)	-1.0 (-2.3, 0.3)	0.4 (-1.1, 2.0)	-1.4 (-2.8, -0.0)
Level 3 (>3 inc. from BL)	4/707 (0.6)	7/668 (1.0)	10/662 (1.5)	-0.9 (-2.0, 0.1)	-0.5 (-1.7, 0.7)	-0.5 (-1.4, 0.5)
Platelets, low (cells/uL)						
Level 1 (<140000)	15/870 (1.7)	26/862 (3.0)	31/858 (3.6)	-1.9 (-3.4, -0.4)	-0.6 (-2.3, 1.1)	-1.3 (-2.7, 0.1)
Level 2 (<125000)	9/870 (1.0)	14/862 (1.6)	18/858 (2.1)	-1.1 (-2.2, 0.1)	-0.5 (-1.8, 0.8)	-0.6 (-1.7, 0.5)
Level 3 (<100000)	2/870 (0.2)	3/862 (0.3)	5/858 (0.6)	-0.4 (-1.0, 0.2)	-0.2 (-0.9, 0.4)	-0.1 (-0.6, 0.4)
WBC Differential						
Lymphocytes, low (cells/uL)						
Level 1 (<1000)	34/870 (3.9)	33/861 (3.8)	45/857 (5.3)	-1.3 (-3.3, 0.6)	-1.4 (-3.4, 0.6)	0.1 (-1.7, 1.9)
Level 2 (<750)	9/870 (1.0)	5/861 (0.6)	13/857 (1.5)	-0.5 (-1.5, 0.6)	-0.9 (-1.9, 0.0)	0.5 (-0.4, 1.3)
Level 3 (<500)	1/870 (0.1)	0/861 (0)	2/857 (0.2)	-0.1 (-0.5, 0.3)	-0.2 (-0.6, 0.1)	0.1 (-0.1, 0.3)
Lymphocytes, high (cells/uL)						
Level 1 (>4000)	18/870 (2.1)	18/861 (2.1)	23/857 (2.7)	-0.6 (-2.1, 0.8)	-0.6 (-2.0, 0.9)	-0.0 (-1.4, 1.3)
Level 2 (>10000)	0/870 (0)	1/861 (0.1)	0/857 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Level 3 (>20000)	0/870 (0)	1/861 (0.1)	0/857 (0)	0 (0, 0)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)
Neutrophils, low (cells/uL)						
Level 1 (<2000)	117/870 (13.4)	125/860 (14.5)	107/857 (12.5)	1.0 (-2.2, 4.1)	2.0 (-1.2, 5.3)	-1.1 (-4.4, 2.2)
Level 2 (<1000)	21/870 (2.4)	26/860 (3.0)	23/857 (2.7)	-0.3 (-1.8, 1.2)	0.3 (-1.2, 1.9)	-0.6 (-2.1, 0.9)
Level 3 (<500)	3/870 (0.3)	7/860 (0.8)	10/857 (1.2)	-0.8 (-1.6, -0.0)	-0.4 (-1.3, 0.6)	-0.5 (-1.2, 0.2)
Eosinophils, high (cells/uL)						
Level 1 (>650)	19/870 (2.2)	26/861 (3.0)	29/857 (3.4)	-1.2 (-2.8, 0.4)	-0.4 (-2.0, 1.3)	-0.8 (-2.3, 0.7)
Level 2 (>1500)	2/870 (0.2)	3/861 (0.3)	2/857 (0.2)	-0.0 (-0.5, 0.4)	0.1 (-0.4, 0.6)	-0.1 (-0.6, 0.4)
Level 3 (>5000)	0/870 (0)	0/861 (0)	0/857 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Coagulation Studies						
PT, high (sec)						
Level 1 (>1.1X ULN)	96/889 (10.8)	114/887 (12.9)	110/880 (12.5)	-1.7 (-4.7, 1.3)	0.4 (-2.8, 3.5)	-2.1 (-5.1, 0.9)
Level 2 (>1.3X ULN)	13/889 (1.5)	14/887 (1.6)	11/880 (1.2)	0.2 (-0.9, 1.3)	0.3 (-0.8, 1.4)	-0.1 (-1.3, 1.0)
Level 3 (>1.5X ULN)	7/889 (0.8)	2/887 (0.2)	7/880 (0.8)	-0.0 (-0.8, 0.8)	-0.6 (-1.2, 0.1)	0.6 (-0.1, 1.2)

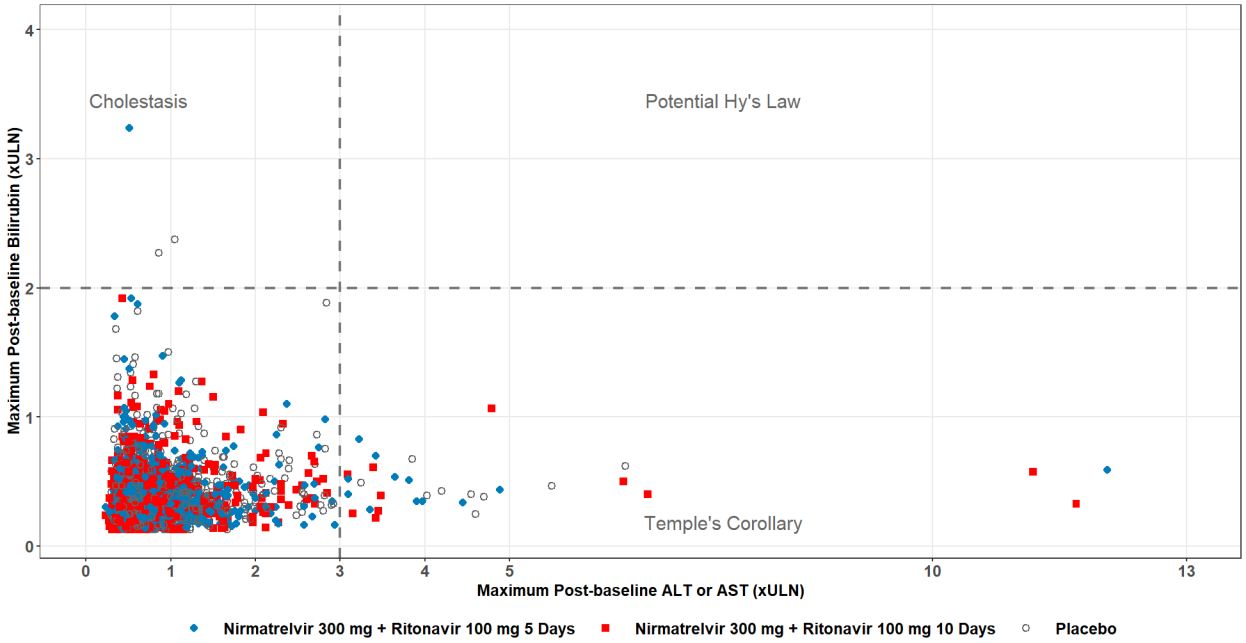
Laboratory Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)[3]
PTT, high (sec)						
Level 1 (>1X ULN)	557/888 (62.7)	523/888 (58.9)	541/878 (61.6)	1.1 (-3.4, 5.6)	-2.7 (-7.3, 1.8)	3.8 (-0.7, 8.4)
Level 2 (>1.21X ULN)	161/888 (18.1)	156/888 (17.6)	161/878 (18.3)	-0.2 (-3.8, 3.4)	-0.8 (-4.3, 2.8)	0.6 (-3.0, 4.1)
Level 3 (>1.41X ULN)	44/888 (5.0)	50/888 (5.6)	43/878 (4.9)	0.1 (-2.0, 2.1)	0.7 (-1.3, 2.8)	-0.7 (-2.8, 1.4)

Source: adlb.xpt; Software: R.
Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (August 2022).
[2.] Duration of treatment is 5 or 10 days.
[3.] Difference is shown between PAXLOVID vs placebo.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell

17.11. Assessment of Drug-Induced Liver Injury, EPIC-PEP

An assessment of DILI for EPIC-PEP was provided in Section 7.6.2.7. Figure 68 and Figure 69 shows a screening assessment for potential cases of serious DILI, whereas Table 167 and Table 168 provide analyses by quadrant for each screening assessment.

Figure 68. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-PEP



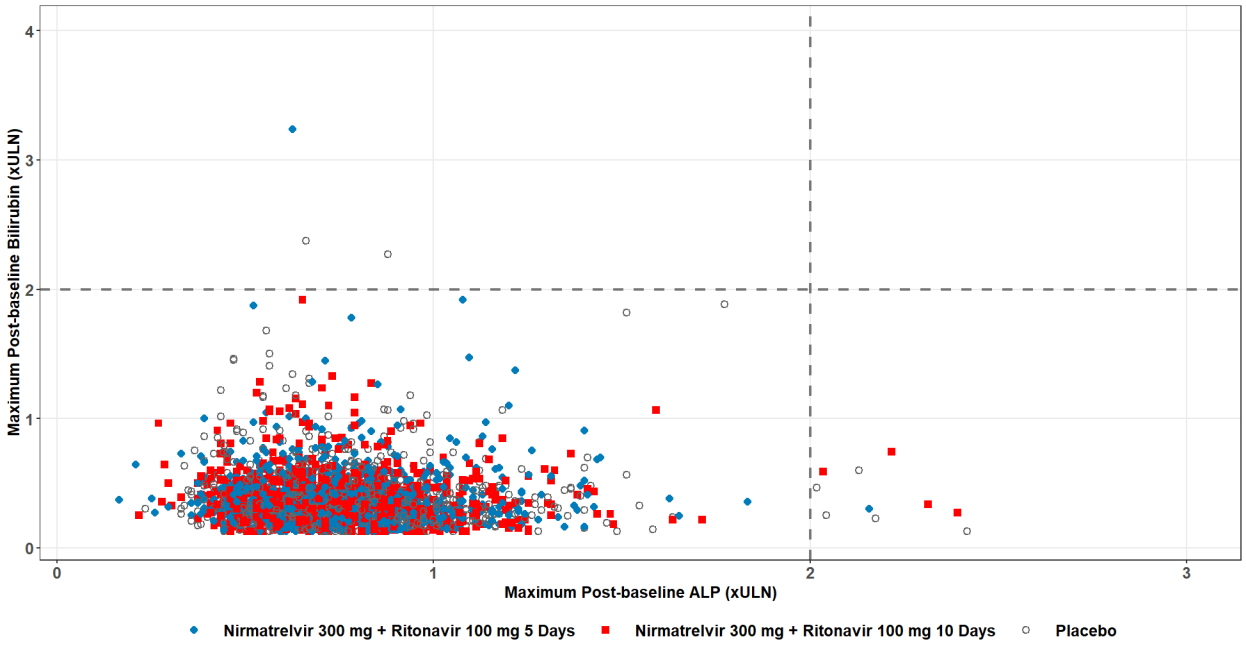
Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
Note: A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All patients with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 167. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, EPIC-PEP

Quadrant	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Potential Hy's Law (right upper)	0/893 (0)	0/891 (0)	0/882 (0)
Cholestasis (left upper)	1/893 (0.1)	0/891 (0)	2/882 (0.2)
Temple's corollary (right lower)	12/893 (1.3)	11/891 (1.2)	9/882 (1)
Total	13/893 (1.5)	11/891 (1.2)	11/882 (1.2)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data

Figure 69. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, EPIC-PEP



Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the post-baseline period.
Note: A potential cholestatic DILI case (red circled) was defined as having a maximum post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after post-baseline ALP became equal to or exceeding 2X ULN.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 168. Patients in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, EPIC-PEP

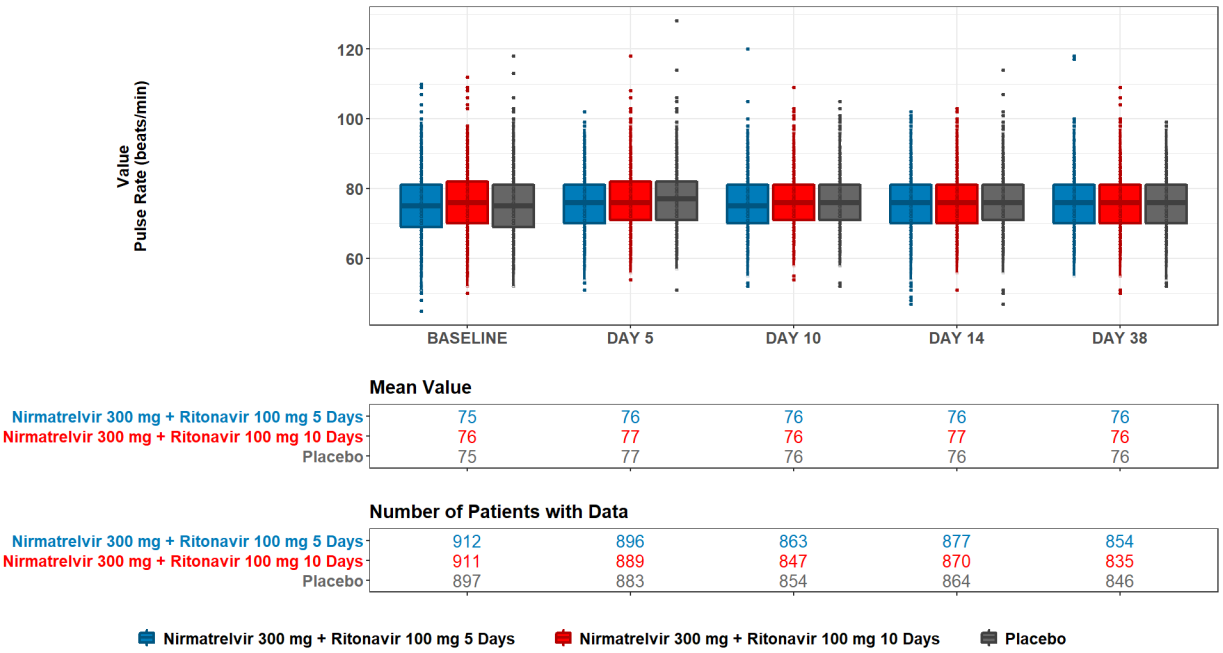
Quadrant	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Bilirubin ≥2X ULN and ALP ≥2X ULN (right upper)	0/893 (0)	0/891 (0)	0/882 (0)
Bilirubin ≥2X ULN and ALP <2X ULN (left upper)	1/893 (0.1)	0/891 (0)	2/882 (0.2)
Bilirubin <2X ULN and ALP ≥2X ULN (right lower)	1/893 (0.1)	4/891 (0.4)	5/882 (0.6)
Total	2/893 (0.2)	4/891 (0.4)	7/882 (0.8)

Source: adlb.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

17.12. Vital Sign Assessment, EPIC-PEP

An overview of vital signs was provided in Section 7.6.2.8. Figure 70, Figure 71, and Figure 72 describe pulse rate, temperature, and respiratory rate in EPIC-PEP.

Figure 70. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, Safety Population, EPIC-PEP



Mean Value

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	75	76	76	76	76
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	76	77	76	77	76
Placebo	75	77	76	76	76

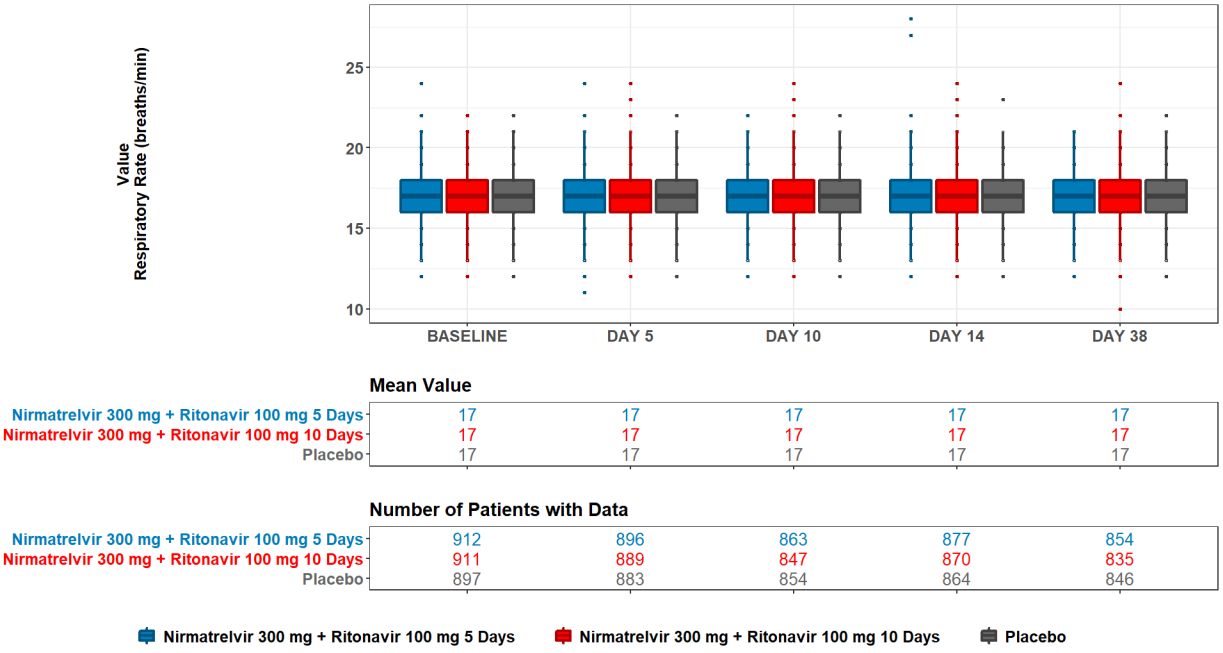
Number of Patients with Data

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	912	896	863	877	854
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	911	889	847	870	835
Placebo	897	883	854	864	846

Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days Placebo

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

Figure 71. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, Safety Population, EPIC-PEP



Mean Value

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	17	17	17	17	17
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	17	17	17	17	17
Placebo	17	17	17	17	17

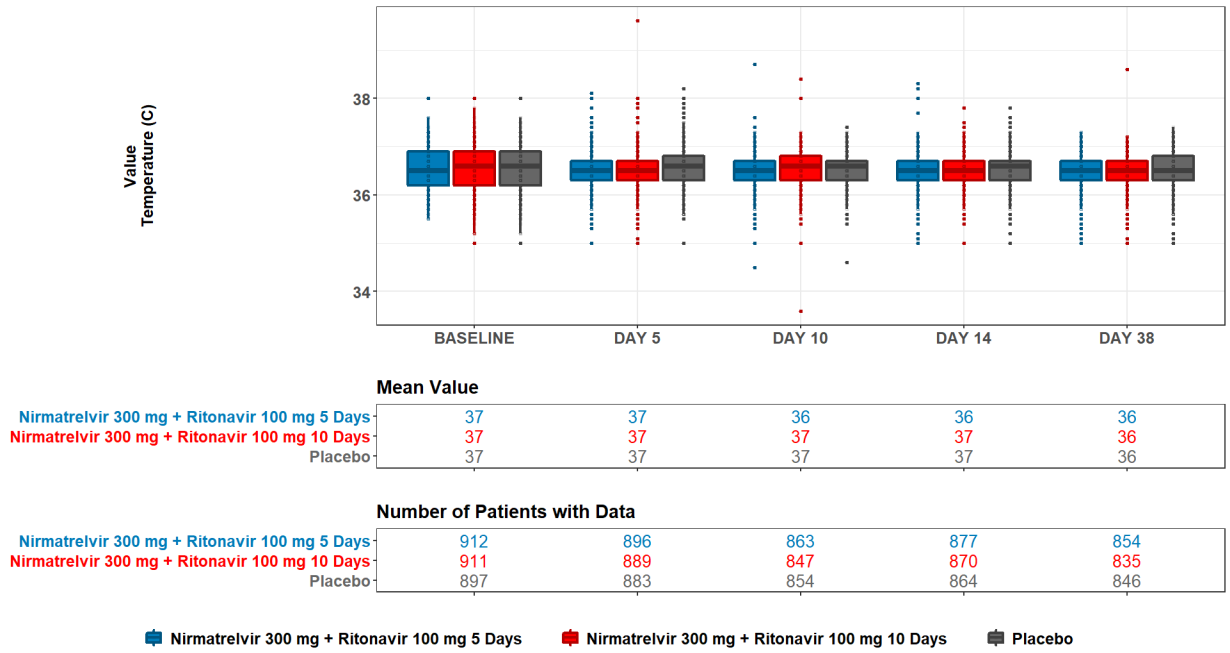
Number of Patients with Data

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	912	896	863	877	854
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	911	889	847	870	835
Placebo	897	883	854	864	846

Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days Placebo

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

Figure 72. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, Safety Population, EPIC-PEP



Mean Value

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	37	37	36	36	36
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	37	37	37	37	36
Placebo	37	37	37	37	36

Number of Patients with Data

	BASELINE	DAY 5	DAY 10	DAY 14	DAY 38
Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days	912	896	863	877	854
Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days	911	889	847	870	835
Placebo	897	883	854	864	846

Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days Placebo

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

17.13. Demographic Subgroup Analysis, EPIC-PEP

An overview of adverse events by demographic subgroups in EPIC-PEP was presented in Section 7.6.2.9. Table 169 summarizes the AEs of demographic subgroups and Table 170 summarizes the SAEs.

Table 169. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial EPIC-PEP

Characteristic	PAXLOVID 5 Days N=912 n/N_s (%)	PAXLOVID 10 Days N=911 n/N_s (%)	Placebo N=898 n/N_s (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Sex, n (%)						
Female	118/499 (23.6)	112/478 (23.4)	104/473 (22.0)	1.7 (-3.6, 6.9)	1.4 (-3.9, 6.8)	0.2 (-5.1, 5.5)
Male	100/413 (24.2)	100/433 (23.1)	91/425 (21.4)	2.8 (-2.9, 8.5)	1.7 (-3.9, 7.2)	1.1 (-4.6, 6.8)
Age group, years, n (%)						
18 to 44	119/475 (25.1)	118/526 (22.4)	109/509 (21.4)	3.6 (-1.6, 8.9)	1.0 (-4.0, 6.1)	2.6 (-2.7, 7.9)
45 to 59	74/297 (24.9)	62/249 (24.9)	61/279 (21.9)	3.1 (-3.9, 10.0)	3.0 (-4.2, 10.3)	0.0 (-7.3, 7.3)
60 to 64	7/61 (11.5)	9/53 (17.0)	8/44 (18.2)	-6.7 (-20.6, 7.2)	-1.2 (-16.4, 14.0)	-5.5 (-18.4, 7.4)
65 to 74	11/50 (22.0)	16/58 (27.6)	13/49 (26.5)	-4.5 (-21.4, 12.3)	1.1 (-15.8, 17.9)	-5.6 (-21.8, 10.7)
≥75	7/29 (24.1)	7/25 (28.0)	4/17 (23.5)	0.6 (-24.9, 26.1)	4.5 (-22.3, 31.2)	-3.9 (-27.4, 19.6)
Age group ≥65, years, n (%)						
≥65	18/79 (22.8)	23/83 (27.7)	17/66 (25.8)	-3.0 (-17.0, 11.1)	2.0 (-12.3, 16.2)	-4.9 (-18.3, 8.4)
Race, n (%)						
American Indian or Alaska Native	16/58 (27.6)	13/52 (25.0)	8/49 (16.3)	11.3 (-4.2, 26.7)	8.7 (-7.0, 24.3)	2.6 (-13.9, 19.0)
Asian	4/8 (50.0)	3/15 (20.0)	7/11 (63.6)	-13.6 (-58.5, 31.2)	-43.6 (-78.5, -8.7) *	30.0 (-10.1, 70.1)
Black or African American	32/137 (23.4)	34/134 (25.4)	36/131 (27.5)	-4.1 (-14.5, 6.3)	-2.1 (-12.7, 8.5)	-2.0 (-12.2, 8.2)
Multiple	0/1 (0)	0/1 (0)	0/1 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Unknown	0/1 (0)	1/1 (100)	0/0 (NA)	NA	NA	-100.0 (-100.0, -100.0)
White	166/707 (23.5)	160/707 (22.6)	144/705 (20.4)	3.1 (-1.3, 7.4)	2.2 (-2.1, 6.5)	0.8 (-3.5, 5.2)
Missing	0/0 (NA)	1/1 (100)	0/1 (0)	NA	100.0 (100.0, 100.0)	NA
Ethnicity, n (%)						
Hispanic or Latino	118/657 (18.0)	109/638 (17.1)	104/642 (16.2)	1.8 (-2.3, 5.9)	0.9 (-3.2, 5.0)	0.9 (-3.3, 5.0)
Not Hispanic or Latino	100/255 (39.2)	103/273 (37.7)	91/256 (35.5)	3.7 (-4.7, 12.1)	2.2 (-6.0, 10.4)	1.5 (-6.8, 9.8)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Note: Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 170. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Trial EPIC-PEP

Characteristic	PAXLOVID 5 Days N=912 n/N_s (%)	PAXLOVID 10 Days N=911 n/N_s (%)	Placebo N=898 n/N_s (%)	PAXLOVID 5 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 10 Days vs Placebo Risk Difference (%) (95% CI)	PAXLOVID 5 Days vs PAXLOVID 10 Days Risk Difference (%) (95% CI)
Sex, n (%)						
Female	3/499 (0.6)	1/478 (0.2)	0/473 (0)	0.6 (-0.1, 1.3)	0.2 (-0.2, 0.6)	0.4 (-0.4, 1.2)
Male	0/413 (0)	0/433 (0)	2/425 (0.5)	-0.5 (-1.1, 0.2)	-0.5 (-1.1, 0.2)	0 (0, 0)
Age group, years, n (%)						
18 to 44	1/475 (0.2)	0/526 (0)	1/509 (0.2)	0.0 (-0.5, 0.6)	-0.2 (-0.6, 0.2)	0.2 (-0.2, 0.6)
45 to 59	1/297 (0.3)	0/249 (0)	0/279 (0)	0.3 (-0.3, 1.0)	0 (0, 0)	0.3 (-0.3, 1.0)
60 to 64	0/61 (0)	0/53 (0)	1/44 (2.3)	-2.3 (-6.7, 2.1)	-2.3 (-6.7, 2.1)	0 (0, 0)
65 to 74	0/50 (0)	1/58 (1.7)	0/49 (0)	0 (0, 0)	1.7 (-1.6, 5.1)	-1.7 (-5.1, 1.6)
≥75	1/29 (3.4)	0/25 (0)	0/17 (0)	3.4 (-3.2, 10.1)	0 (0, 0)	3.4 (-3.2, 10.1)
Age group ≥65, years, n (%)						
≥65	1/79 (1.3)	1/83 (1.2)	0/66 (0)	1.3 (-1.2, 3.7)	1.2 (-1.1, 3.6)	0.1 (-3.3, 3.5)
Race, n (%)						
American Indian or Alaska Native	0/58 (0)	0/52 (0)	0/49 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Asian	0/8 (0)	0/15 (0)	0/11 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Black or African American	0/137 (0)	0/134 (0)	0/131 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Multiple	0/1 (0)	0/1 (0)	0/1 (0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Unknown	0/1 (0)	0/1 (0)	0/0 (NA)	NA	NA	0 (0, 0)
White	3/707 (0.4)	1/707 (0.1)	2/705 (0.3)	0.1 (-0.5, 0.8)	-0.1 (-0.6, 0.3)	0.3 (-0.3, 0.8)
Missing	0/0 (NA)	0/1 (0)	0/1 (0)	NA	0 (0, 0)	NA
Ethnicity, n (%)						
Hispanic or Latino	2/657 (0.3)	0/638 (0)	0/642 (0)	0.3 (-0.1, 0.7)	0 (0, 0)	0.3 (-0.1, 0.7)
Not Hispanic or Latino	1/255 (0.4)	1/273 (0.4)	2/256 (0.8)	-0.4 (-1.7, 0.9)	-0.4 (-1.7, 0.9)	0.0 (-1.0, 1.1)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

17.14. Adverse Events of Special Interest

17.14.1. Thyroid-related events

This section provides additional details for the adverse events of special interest (AESI) of thyroid-related events. As summarized in Section 7.6.3.1, frequencies of any thyroid-related AEs were similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 171).

There was one severe (Grade 3) event of blood thyroid stimulating hormone increase in subject (b) (6) in EPIC-PEP who was a 20-year-old male in the PAXLOVID 5-day group who had a thyrotropin within reference range at baseline. This AE was reported on Day 5 with a thyrotropin of 4.81 mIU/L (reference range: 0.53 to 3.59 mIU/L) and was reported resolved on Day 10. The investigator assessed the causality of this AE as not related to study intervention; however, it was reported to be related to "other: unknown".

Abnormalities in the laboratory test for thyrotropin (>1.2x ULN) were more frequent in the PAXLOVID 5-day (38/829, 4.6%) and 10-day (35/827, 4.2%) groups when compared to the placebo group (33/843, 3.9%).

Table 171. Thyroid-Related Adverse Event Assessment[1], Safety Population, Trials EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Thyroid-Related AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any thyroid-related AE	6 (0.6)	7 (0.7)	3 (0.6)	5 (0.9)	9 (0.6)	12 (0.8)
Blood thyroid stimulating hormone increased	5 (0.5)	7 (0.7)	2 (0.4)	5 (0.9)	7 (0.4)	12 (0.8)
Thyroxine free increased	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Thyroxine increased	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Maximum severity						
Moderate	0	3 (0.3)	0	0	0	3 (0.2)
Mild	6 (0.6)	5 (0.5)	3 (0.6)	6 (1.1)	9 (0.6)	11 (0.7)
Serious event	0	0	0	0	0	0
Resulted in discontinuation	0	0	0	0	0	0
Relatedness[3]	1 (0.1)	3 (0.3)	2 (0.4)	4 (0.8)	3 (0.2)	7 (0.4)

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

In EPIC-PEP, the frequencies of thyroid-related AEs of blood thyroid stimulating hormone increased and thyroxine free decreased were similar between all groups (1.2% in the 5-day PAXLOVID group, 0.9% in the 10-day group, and 1.1% in the placebo group).

17.14.2. Inflammatory Events

This section provides additional details for the AESI of inflammatory events. As summarized in Section 7.6.3.2, any inflammatory-related AE was similar between the PAXLOVID group and placebo group in EPIC-HR and EPIC-SR (Table 172). Frequencies of inflammatory related AEs graded as severe or life-threatening were also similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 172). Details regarding these events are described in Table 173. Table 174 describes inflammatory-related laboratory outliers.

The incidence of all-causality AEs was comparable between treatment groups, except for Fibrin D dimer increases and activated partial thromboplastin time prolongation, which occurred at greater frequencies (≥5 subjects) in the placebo group compared with the PAXLOVID group in EPIC-HR and the pooled trials. Severe or life-threatening events were reported infrequently (0.6% in the pooled PAXLOVID groups) and none of these resulted in death. The SAE of D-dimer increase was reported in Subject (b) (6) in EPIC-HR who received placebo. This event occurred on Day 8 and resolved. In terms of laboratory outliers, leukocytes >1.5x ULN and neutrophils >1.2x ULN occurred at greater frequency (≥5 subjects) in the PAXLOVID group when compared to placebo in EPIC-HR. Neutrophils >1.2x ULN and lymphocytes >1.2x ULN occurred at greater frequencies (≥5 subjects) in the PAXLOVID group compared to placebo in the pooled analysis. Other hematology related laboratory outliers were similar or occurred at a higher frequency in the placebo group when compared to the PAXLOVID group. In EPIC-PEP, events were similar except for fibrin D dimer increases which occurred at greater frequency (≥5 subjects) in the PAXLOVID group when compared to placebo. Few subjects had severe (Grade 3) or higher inflammatory-related AEs. Frequency of inflammatory-related laboratory outliers were similar between all treatment groups.

Table 172. Inflammatory-Related Adverse Events Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Inflammatory-Related AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any inflammatory-related AE	42 (4.0)	45 (4.3)	14 (2.6)	14 (2.7)	56 (3.5)	59 (3.7)
Activated partial thromboplastin time prolonged	9 (0.9)	12 (1.1)	3 (0.6)	6 (1.1)	12 (0.8)	18 (1.1)
Blood fibrinogen increased	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
C-reactive protein increased	10 (1.0)	13 (1.2)	3 (0.6)	2 (0.4)	13 (0.8)	15 (0.9)
Fibrin D dimer increased	22 (2.2)	30 (2.8)	6 (1.1)	6 (1.1)	28 (1.8)	36 (2.3)
Haptoglobin increased	4 (0.4)	3 (0.3)	0	0	4 (0.3)	3 (0.2)
Leukocytosis	2 (0.2)	0	0	0	2 (0.1)	0
Platelet count increased	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Prothrombin time prolonged	3 (0.3)	5 (0.5)	2 (0.4)	0	5 (0.3)	5 (0.3)
White blood cell count increased	2 (0.2)	0	0	0	2 (0.1)	0
Maximum severity						
Life-threatening	2 (0.2)	2 (0.2)	0	0	2 (0.1)	2 (0.1)
Severe	7 (0.7)	8 (0.8)	0	0	7 (0.4)	8 (0.5)
Moderate	13 (1.3)	15 (1.4)	2 (0.4)	5 (0.9)	15 (1.0)	20 (1.3)
Mild	32 (3.1)	39 (3.7)	13 (2.4)	10 (1.9)	45 (2.9)	49 (3.1)
Serious	0	1(0.1)	0	0	0	1(0.1)
Deaths	0	1(0.1)	0	0	0	1(0.1)

	EPIC-HR		EPIC-SR		Pooled	
Inflammatory-Related AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Resulting in discontinuation	0	0	0	0	0	0
Relatedness[3]	1 (0.1)	3 (0.3)	2 (0.4)	0	3 (0.2)	3 (0.2)

Source: adae.xpt; Software: JMP
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 173. Subjects With Severe (Grade 3) or Life-Threatening (Grade 4) Inflammatory-Related AE[1], EPIC-HR and EPIC-SR[2]

Subject Identifier	Treatment	Age	Sex	Dictionary-Derived Term	Study Day of AE Onset	Outcome of AE	Related[3]	SAE
(b) (6)	Placebo	49	F	Fibrin D dimer increased	15	Recovered/resolved	N	N
	Placebo	49	F	Fibrin D dimer increased	20	Recovered/resolved	N	N
	PAXLOVID	43	M	Fibrin D dimer increased	5	Recovered/resolved	N	N
	PAXLOVID	73	M	Prothrombin time prolonged	6	Recovered/resolved	N	N
	Placebo	39	M	Fibrin D dimer increased	5	Recovered/resolved	N	N
	PAXLOVID	70	F	C-reactive protein increased	1	Recovered/resolved	N	N
	Placebo	46	M	C-reactive protein increased	1	Recovered/resolved	N	N
	Placebo	47	M	Activated partial thromboplastin time prolonged	1	Recovering/resolving	N	N
	PAXLOVID	40	M	C-reactive protein increased	6	Recovered/resolved	N	N
	Placebo	68	F	Prothrombin time prolonged	6	Recovering/resolving	N	N
	PAXLOVID	72	F	Activated partial thromboplastin time prolonged	1	Recovering/resolving	N	N
	PAXLOVID	79	F	Fibrin D dimer increased	14	Recovering/resolving	N	N
	Placebo	62	M	Prothrombin time prolonged	14	Recovering/resolving	N	N
	Placebo	61	M	Activated partial thromboplastin time prolonged	1	Recovered/resolved	N	N
	Placebo	68	F	Fibrin D dimer increased	1	Recovered/resolved	N	N
	PAXLOVID	69	F	Prothrombin time prolonged	1	Recovered/resolved	N	N
	Placebo	70	F	Fibrin D dimer increased	8	Recovered/resolved	N	Y
	PAXLOVID	76	F	Fibrin D dimer increased	1	Recovered/resolved	N	N
	PAXLOVID	81	F	Fibrin D dimer increased	1	Recovered/resolved	N	N

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; F, female; M, male; N, no; SAE, serious adverse event; Y, yes

Table 174. Inflammatory Related Laboratory Outliers, Safety Population, EPIC-HR and EPIC-SR[1]

		EPIC-HR		EPIC-SR		Pooled	
Parameter	**Outlier**	**PAXLOVID N=1038 n/N_w (%)**	**Placebo N=1053 n/N_w (%)**	**PAXLOVID N=540 n/N_w (%)**	**Placebo N=528 n/N_w (%)**	**PAXLOVID N=1578 n/N_w (%)**	**Placebo N=1581 n/N_w (%)**
Activated partial thromboplastin time (sec)	>1.1x ULN	183/928 (19.7)	181/942 (19.2)	88/513 (17.2)	88/498 (17.7)	271/1441 (18.8)	269/1440 (18.7)
D-Dimer (ng/mL)	>1.5x ULN	120/975 (12.3)	186/988 (18.8)	39/522 (7.5)	47/520 (9.0)	159/1497 (10.6)	233/1508 (15.5)
Eosinophils (10^9/L)	>1.2x ULN	7/870 (0.8)	9/882 (1.0)	0/547 (0.0)	2/441 (0.5)	7/1417 (0.5)	11/1323 (0.8)
Leukocytes (10^9/L)	<0.6x LLN	1/873 (0.1)	9/890 (1.0)	1/461 (0.2)	2/446 (0.4)	2/1334 (0.1)	11/1336 (0.8)
	>1.5x ULN	13/873 (1.5)	10/890 (1.1)	2/461 (0.4)	4/446 (0.9)	15/1334 (1.1)	13/1336 (1.0)
Lymphocytes (10^9/L)	<0.8x LLN	18/870 (2.1)	42/882 (4.8)	5/457 (1.1)	7/441 (1.6)	23/1327 (1.7)	49/1323 (3.7)
	>1.2x ULN	9/870 (1.0)	8/882 (0.9)	4/457 (0.9)	0/441 (0.0)	13/1327 (1.0)	8/1323 (0.6)
Neutrophils (10^9/L)	<0.8x LLN	24/866 (2.8)	43/881 (4.9)	14/455 (3.1)	19/439 (4.3)	38/1321 (2.9)	62/1320 (4.7)
	>1.2x ULN	55/866 (6.4)	33/881 (3.7)	12/455 (2.6)	9/439 (2.1)	67/1321 (5.1)	41/1320 (3.1)
Platelets (10^9/L)	<0.5x LLN	0/864 (0.0)	4/884 (0.5)	0/456 (0.0)	0/439 (0.0)	0/1320 (0.0)	4/1323 (0.3)
	>1.75x ULN	5/864 (0.6)	10/884 (1.1)	0/456 (0.0)	1/439 (0.2)	5/1320 (0.4)	11/1323 (0.8)
Prothrombin intl. normalized ratio	>1.1x ULN	49/931 (5.3)	51/942 (5.4)	13/513 (2.5)	12/498 (2.4)	62/1444 (4.3)	63/1440 (4.4)
Prothrombin time (sec)	>1.1x ULN	92/931 (9.9)	106/942 (11.3)	14/513 (2.7)	12/498 (2.4)	106/1444 (7.3)	118/1440 (8.2)
Fibrinogen (mg/dL)	<0.75x Baseline	311/974 (31.9)	284/997 (28.5)	160/524 (30.5)	138/504 (27.4)	471/1498 (31.4)	422/1501 (28.1)
	>1.25x Baseline	160/974 (16.4)	238/988 (24.1)	78/524 (14.9)	87/504 (17.3)	238/1498 (15.9)	325/1492 (21.8)

Source: adlb.xpt; Software: JMP
[1]Duration of treatment is 5 days
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w: number of patients with data; ULN, upper limit of normal; LLN, lower limit of normal

As summarized in Section 7.6.3.2, any inflammatory-related AE was similar between the PAXLOVID groups and placebo group in EPIC-PEP (Table 175). Frequencies of inflammatory related AEs graded as severe or life-threatening were also similar between the PAXLOVID and placebo groups in EPIC-PEP (Table 175). Details regarding these events are described in Table 176. Table 177 describes inflammatory-related laboratory outliers in EPIC-PEP.

Table 175. Inflammatory-Related Adverse Events Assessment[1], Safety Population, EPIC-PEP[2]

Inflammatory-related AE assessment	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Any Inflammatory-related AE	31 (3.4)	31 (3.4)	31 (3.5)
Activated partial thromboplastin time prolonged	11 (1.2)	14 (1.5)	22 (2.4)
C-reactive protein increased	0	1 (0.1)	4 (0.4)
Eosinophilia	1 (0.1)	1 (0.1)	0
Fibrin D dimer increased	18 (2.0)	13 (1.4)	4 (0.4)
Haptoglobin increased	0	0	1 (0.1)
Platelet count increased	0	0	1 (0.1)
Prothrombin time prolonged	3 (0.3)	4 (0.4)	3 (0.3)
Maximum Severity			
Severe	2 (0.2)	0	2 (0.2)
Moderate	8 (0.9)	8 (0.9)	4 (0.4)
Mild	23 (2.5)	25 (2.7)	29 (3.2)
Serious	0	0	0
Resulting in discontinuation	1 (0.1)	0	1 (0.1)
Relatedness[3]	7 (0.8)	13 (1.4)	9 (1.0)

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 176. Subjects With Severe (Grade 3) or Life-Threatening (Grade 4) Inflammatory-Related Adverse Events[1], EPIC-PEP[2]

Unique Subject Identifier	Treatment	Age	Sex	Dictionary-Derived Term	Study Day of AE Onset	Outcome of AE	Related[3]	SAE
(b) (6)	Placebo	67	M	Fibrin D dimer increased	1	Recovered/resolved	N	N
	Placebo	40	F	C-reactive protein increased	1	Recovered/resolved	N	N
	PAXLOVID 5 Days	34	F	Fibrin D dimer increased	1	Recovering/resolving	N	N
	PAXLOVID 10 Days	82	F	Activated partial thromboplastin time prolonged	8	Recovered/resolved	Y	N

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: F, female; M, male; N, no; SAE, serious adverse event; Y, yes

Table 177. Inflammatory Related Laboratory Outliers, Safety Population, Trial EPIC-PEP[1]

Parameter	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
Activated Partial Thromboplastin Time (sec)			
>1.1x ULN	337/888 (38.0)	319/888 (35.9)	318/878 (36.2)
Basophils (10^9/L)			
>1.2x ULN	1/870 (0.1)	0/861	0/857
D-Dimer (ng/mL)			
>1.5x ULN	74/893 (8.3)	62/889 (7.0)	71/879 (8.1)
Eosinophils (10^9/L)			
>1.2x ULN	7/870 (0.8)	11/861 (1.3)	9/857 (1.1)
Fibrinogen (mg/dL)			
>1.25x Baseline	184/894 (20.6)	195/889 (21.9)	195/880 (22.2)
<0.75x Baseline	227/894 (25.4)	239/889 (26.9)	220/880 (25.0)
Leukocytes (10^9/L)			
>1.5x ULN	2/871 (0.2)	0/863	2/859 (0.2)
<0.6x LLN	5/871 (0.6)	4/863 (0.5)	6/859 (0.7)
Lymphocytes (10^9/L)			
>1.2x ULN	9/871 (1.0)	9/863 (1.0)	10/859 (1.2)
<0.8x LLN	7/870 (0.8)	5/861 (0.6)	11/857 (1.3)
Monocytes (10^9/L)			
>1.2x ULN	3/870 (0.3)	2/861 (0.2)	0/857
Neutrophils (10^9/L)			
>1.2x ULN	18/870 (2.1)	13/860 (1.5)	14/857 (1.6)
<0.8x LLN	40/870 (4.6)	49/860 (5.7)	39/857 (4.6)
Platelets (10^9/L)			
>1.75x ULN	0/870	1/862 (0.1)	2/858 (0.2)
<0.5x LLN	0/870	2/862 (0.2)	2/858 (0.2)
Prothrombin Intl. Normalized Ratio			
>1.1x ULN	41/889 (4.6)	47/887 (5.3)	37/880 (4.2)
Prothrombin Time (sec)			
>1.1x ULN	96/889 (10.8)	114/887 (12.9)	110/880 (12.5)

Source: adlb.xpt; Software: JMP.
[1.] Duration of treatment is 5 or 10 days.
Abbreviations: Intl, international; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw: number of patients with data; ULN, upper limit of normal; LLN, lower limit of normal

17.14.1. Hypersensitivity Events

The instances of rash in EPIC-HR and EPIC-SR are described below:

- Subject (b) (6): in EPIC-HR received PAXLOVID experienced severe (Grade 3) rash maculo-papular on Day 2 and the study drug was subsequently discontinued. This event was reported as resolved on Day 3 and the investigator assessed this event as related to study intervention.
- Subject (b) (6): in EPIC-HR received PAXLOVID and experienced mild (Grade 1) rash on Day 2 and subsequently treated with hydroxyzine hydrochloride. No modifications were

made to study intervention and the event was reported as resolved on Day 3. The investigator assessed this event was related to study intervention.

- Subject [redacted] (b) (6): in EPIC-HR received PAXLOVID and experienced mild (Grade 1) rash and mild (Grade 1) pruritus on Day 2. The participant continued study intervention and these adverse events were reported as resolved on Day 54.

17.14.2. Hepatoxicity

This section provides additional details for the AESI of hepatotoxicity. As summarized in Section 7.6.3.4, frequencies of hepatic related AEs were low and comparable between the PAXLOVID and placebo groups in all three trials. Table 178 describes hepatobiliary AEs in EPIC-HR and EPIC-SR, Table 179 describes drug-induced liver injury assessment in EPIC-HR and EPIC-SR, and Table 180 describes hepatobiliary AEs in the subset of vaccinated participants with at least one risk factor for progression to severe disease in EPIC-SR.

Table 178. Hepatobiliary SOC Adverse Events Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Hepatobiliary Disorders AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any Hepatobiliary disorders AE	4 (0.4)	2 (0.2)	1 (0.2)	1 (0.2)	5 (0.3)	3 (0.2)
Cholestasis	1 (0.1)	0	0	0	1 (0.1)	0
Hepatic function abnormal	1 (0.1)	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Hepatic mass	0	0	1 (0.2)	0	1 (0.1)	0
Hepatitis toxic	1 (0.1)	0	0	0	1 (0.1)	0
Hyperbilirubinemia	1 (0.1)	0	0	0	1 (0.1)	0
Liver injury	0	1 (0.1)	0	0	0	1 (0.1)
Maximum severity						
Severe	1 (0.1)	0	0	0	1 (0.1)	0
Moderate	2 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.2)	2 (0.1)
Mild	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Serious	0	0	1 (0.2)	0	1 (0.1)	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0
Relatedness[3]	0	0	0	0	0	0

Source: adae.xpt; Software: JMP.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of patients in treatment arm; n, number of patients with adverse event

Table 179. Drug-Induced Liver Injury Assessment[1], Safety Population, EPIC-HR and EPIC-SR[2]

	EPIC-HR		EPIC-SR		Pooled	
Drug-Induced Liver Injury Assessment	**PAXLOVID N=1038 n (%)**	**Placebo N=1053 n (%)**	**PAXLOVID N=540 n (%)**	**Placebo N=528 n (%)**	**PAXLOVID N=1578 n (%)**	**Placebo N=1581 n (%)**
AE grouping related to AESI	17 (1.6)	30 (2.8)	13 (2.4)	9 (1.7)	30 (1.9)	39 (2.5)
Alanine aminotransferase inc.	17 (1.6)	27 (2.6)	13 (2.4)	8 (1.5)	30 (1.9)	35 (2.2)
Aspartate aminotransferase inc.	10 (1.0)	14 (1.3)	7 (1.3)	4 (0.8)	17 (1.1)	18 (1.1)
Cholestasis	1 (0.1)	0	0	0	1 (0.06)	0
Liver injury	0	1 (0.09)	0	0	0	1 (0.06)
Maximum severity						
Life-threatening	0	1 (0.09)	1 (0.2)	0	1 (0.06)	1 (0.06)
Severe	2 (0.2)	5 (0.5)	1 (0.2)	0	3 (0.2)	5 (0.3)
Moderate	15 (1.4)	20 (1.9)	7 (1.3)	6 (1.1)	22 (1.4)	26 (1.6)
Mild	0	4 (0.4)	4 (0.7)	3 (0.6)	4 (0.3)	7 (0.4)
Serious	0	1 (0.09)	0	0	0	1 (0.06)
Deaths	0	0	0	0	0	0
Resulting in discontinuation	1 (0.1)	1 (0.09)	0	0	1 (0.06)	1 (0.06)
Relatedness[3]	5 (0.5)	2 (0.2)	4 (0.7)	1 (0.2)	9 (0.6)	3 (0.2)

Source: adae.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; inc, increased; N, number of patients in treatment arm; n, number of patients with adverse event

Table 180. Adverse Events[1] of Drug-Induced Liver Injury Assessment, Vaccinated Participants With Risk Factors Assessed by the Applicant, Safety Population, EPIC-SR[2]

Drug-Induced Liver Injury Assessment	**PAXLOVID N=317 n (%)**	**Placebo N=314 n (%)**	**Risk Difference (%) (95% CI)[3]**
AE grouping related to AESI	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Alanine aminotransferase inc.	6 (1.9)	4 (1.3)	0.6 (-1.3, 2.6)
Aspartate aminotransferase inc.	4 (1.3)	1 (0.3)	0.9 (-0.4, 2.3)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	1 (0.3)	0	0.3 (-0.3, 0.9)
Moderate	4 (1.3)	4 (1.3)	-0.0 (-1.8, 1.7)
Mild	1 (0.3)	0	0.3 (-0.3, 0.9)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)
Relatedness	2 (0.6)	1 (0.3)	0.3 (-0.8, 1.4)

Source: adae.xpt; Software: R.
Note: Participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.
1. Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
2. Duration of treatment is 5 days.
3. Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; inc, increased; N, number of patients in treatment arm; n, number of patients with adverse event

In EPIC-PEP there were three AEs in the hepatobiliary disorders system organ class (SOC). This included one SAE of severe (Grade 3) acute cholecystitis in subject (b) (6), a 47-year-old

female who was in the PAXLOVID 5-day group. This subject experienced the SAE of acute cholecystitis on Day 14. This subject was reported resolved on Day 34 and the subject was subsequently discharged from the hospital. This AE was considered not related to study intervention. The remainder of AEs in the hepatobiliary SOC were mild in severity.

The remainder AEs were one each of mild (Grade 1) non-alcoholic steatohepatitis in the PAXLOVID 5-day group and mild (Grade 1) nonalcoholic fatty liver disease in the PAXLOVID 10-day group. None of the AEs were considered related to study intervention and none resulted in discontinuation of study drug.

In terms of drug-induced liver injury, severe and life-threatening AEs were infrequent, and none were considered SAEs (Table 181). There were no deaths and few cases resulted in discontinuation of study drug.

Table 181. Drug-Induced Liver Injury Assessment[1], Safety Population, EPIC-PEP[2]

Drug-Induced Liver Injury Assessment	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
AE grouping related to AESI	2 (0.2)	7 (0.8)	12 (1.3)
Alanine aminotransferase increased	2 (0.2)	6 (0.7)	11 (1.2)
Aspartate aminotransferase increased	2 (0.2)	5 (0.5)	7 (0.8)
Maximum severity			
Death	0	0	0
Life-threatening	0	2 (0.2)	0
Severe	1 (0.1)	0	1 (0.1)
Moderate	1 (0.1)	2 (0.2)	5 (0.6)
Mild	0	3 (0.3)	6 (0.7)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	1 (0.1)	2 (0.2)
Relatedness[3]	1 (0.1)	4 (0.4)	3 (0.3)

Source: adae.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 38 visit.
[2.] Duration of treatment is 5 or 10 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of patients in treatment arm; n, number of patients with adverse event

17.14.3. Hemodynamic Events

This section provides additional details for the AESI of hemodynamic adverse events. As summarized in Section 7.6.3.4, the frequencies of any hemodynamic AE was similar between the PAXLOVID and placebo groups in EPIC-HR and EPIC-SR (Table 182). Additionally, the frequencies of systolic blood pressure ≥140 mm hg, ≥160 mm hg, and ≥180 mm hg were similar between PAXLOVID and placebo groups (Table 183). Frequencies of diastolic blood pressure ≥90 mm hg, ≥110 mm hg, and ≥120 mm hg were also similar between both groups (Table 184).

Table 182. Hemodynamic Adverse Events Assessment[1], Safety Population, EPIC-SR and EPIC-HR[2]

	EPIC-HR		EPIC-SR		Pooled	
Hemodynamic AE Assessment	**PAXLOVID N=1038 n(%)**	**Placebo N=1053 n(%)**	**PAXLOVID N=540 n(%)**	**Placebo N=528 n(%)**	**PAXLOVID N=1578 n(%)**	**Placebo N=1581 n(%)**
Any hemodynamic AE	8 (0.8)	8 (0.8)	8 (1.5)	8 (1.5)	16 (1.0)	16 (1.0)
Blood pressure decreased	0	0	1 (0.2)	0	1 (0.1)	0
Blood pressure increased	1 (0.1)	1 (0.1)	0	2 (0.4)	1 (0.1)	3 (0.2)
Bradycardia	0	0	0	1 (0.2)	0	1 (0.1)
Heart rate decreased	0	0	1 (0.2)	0	1 (0.1)	0
Hypertension	6 (0.6)	2 (0.2)	2 (0.4)	2 (0.4)	8 (0.5)	4 (0.3)
Hypertensive crisis	1 (0.1)	0	0	0	1 (0.1)	0
Hypotension	1 (0.1)	4 (0.4)	2 (0.4)	0	3 (0.2)	4 (0.3)
Sinus bradycardia	0	1 (0.1)	0	1 (0.2)	0	2 (0.1)
Sinus tachycardia	0	1 (0.1)	0	0	0	1 (0.1)
Tachycardia	0	0	1 (0.2)	3 (0.6)	1 (0.1)	3 (0.2)
Maximum severity						
Life-threatening	1 (0.1)	0	0	0	1 (0.1)	0
Severe	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Moderate	1 (0.1)	4 (0.4)	2 (0.4)	3 (0.6)	3 (0.2)	7 (0.4)
Mild	6 (0.6)	3 (0.3)	6 (1.1)	5 (0.9)	12 (0.8)	8 (0.5)
Serious	1 (0.1)	0	0	0	1 (0.1)	0
Deaths	0	0	0	0	0	0
Relatedness[3]	0	0	1 (0.2)	0	1 (0.1)	0
Resulting in discontinuation	1 (0.1)	0	0	0	1 (0.1)	0

Source: adae.xpt; Software: JMP.
[1.] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit.
[2.] Duration of treatment is 5 days.
[3.] Relatedness is determined by investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 183. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Systolic Blood Pressure (mmHg)	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)
<90	0/1038 (0)	0/1052 (0)	0 (0, 0)	0/540 (0)	0/527 (0)	0 (0, 0)	0/1578 (0)	0/1579 (0)	0 (0, 0)
≥90	1038/1038 (100)	1052/1052 (100)	0 (0, 0)	540/540 (100)	527/527 (100)	0 (0, 0)	1578/1578 (100)	1579/1579 (100)	0 (0, 0)
≥120	933/1038 (89.9)	935/1052 (88.9)	1.0 (-1.6, 3.6)	459/540 (85.0)	450/527 (85.4)	-0.4 (-4.7, 3.9)	1392/1578 (88.2)	1385/1579 (87.7)	0.5 (-1.8, 2.8)
≥140	204/1038 (19.7)	201/1052 (19.1)	0.5 (-2.8, 3.9)	97/540 (18.0)	101/527 (19.2)	-1.2 (-5.9, 3.5)	301/1578 (19.1)	302/1579 (19.1)	-0.1 (-2.8, 2.7)
≥160	12/1038 (1.2)	19/1052 (1.8)	-0.7 (-1.7, 0.4)	8/540 (1.5)	10/527 (1.9)	-0.4 (-2.0, 1.1)	20/1578 (1.3)	29/1579 (1.8)	-0.6 (-1.4, 0.3)
≥180	1/1038 (0.1)	4/1052 (0.4)	-0.3 (-0.7, 0.1)	1/540 (0.2)	5/527 (0.9)	-0.8 (-1.7, 0.1)	2/1578 (0.1)	9/1579 (0.6)	-0.4 (-0.9, -0.0)

Source: advs.xpt; Software: R.
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 184. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-HR and EPIC-SR

	EPIC-HR			EPIC-SR			Pooled		
Diastolic Blood Pressure (mmHg)	PAXLOVID N=1038 n/Nw (%)	Placebo N=1053 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=540 n/Nw (%)	Placebo N=528 n/Nw (%)	Risk Difference (%) (95% CI)	PAXLOVID N=1578 n/Nw (%)	Placebo N=1581 n/Nw (%)	Risk Difference (%) (95% CI)
<60	0/1038	0/1052	0	0/540	0/527	0	0/1578	0/1579	0
	(0)	(0)	(0, 0)	(0)	(0)	(0, 0)	(0)	(0)	(0, 0)
≥60	1038/1038	1052/1052	0	540/540	527/527	0	1578/1578	1579/1579	0
	(100)	(100)	(0, 0)	(100)	(100)	(0, 0)	(100)	(100)	(0, 0)
≥90	243/1038	238/1052	0.8	91/540	126/527	-7.1	334/1578	364/1579	-1.9
	(23.4)	(22.6)	(-2.8, 4.4)	(16.9)	(23.9)	(-11.9, -2.2)	(21.2)	(23.1)	(-4.8, 1.0)
≥110	3/1038	6/1052	-0.3	3/540	3/527	-0.0	6/1578	9/1579	-0.2
	(0.3)	(0.6)	(-0.8, 0.3)	(0.6)	(0.6)	(-0.9, 0.9)	(0.4)	(0.6)	(-0.7, 0.3)
≥120	0/1038	0/1052	0	0/540	1/527	-0.2	0/1578	1/1579	-0.1
	(0)	(0)	(0, 0)	(0)	(0.2)	(-0.6, 0.2)	(0)	(0.06)	(-0.2, 0.1)

Source: advs.xpt; Software: R
Note: Participants enrolled in EPIC-HR at sites 1274 and 1470 (including those switched to 1276) and in EPIC-SR at sites 1281 and 1488 (including those switched to 1282) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

As described in Section 7.6.3.4, in EPIC-PEP, the AE of hypertension was infrequent and occurred at similar frequencies between the 5-day (0.2%), 10-day (0.2%), and placebo (0.1%) groups. One subject experienced moderate (Grade 2) hypertension in the PAXLOVID 10-day group. The remained of instances of hypertension were all mild (Grade 1) in severity. Other hemodynamic AEs in the PAXLOVID 5-day group included one AE of moderate (Grade 2) bradycardia. In the PAXLOVID 10-day group there was one each of loss of consciousness and syncope, all of which were mild (Grade 1) in severity. There were no severe (Grade 3) or higher AEs associated with hemodynamic events in the Safety Population in EPIC-PEP. When evaluating vital signs, frequencies of systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg were similar across all groups (Table 185 and Table 186).

Table 185. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, EPIC-PEP

Systolic Blood Pressure (mmHg)	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
<90	0/905 (0)	0/908 (0)	0/895 (0)
≥90	905/905 (100)	908/908 (100)	895/895 (100)
≥120	792/905 (87.5)	809/908 (89.1)	785/895 (87.7)
≥140	96/905 (10.6)	95/908 (10.5)	89/895 (9.9)
≥160	2/905 (0.2)	13/908 (1.4)	6/895 (0.7)
≥180	1/905 (0.1)	2/908 (0.2)	3/895 (0.3)

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 186. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial EPIC-PEP

Diastolic Blood Pressure (mmHg)	PAXLOVID 5 Days N=912 n/N_w (%)	PAXLOVID 10 Days N=911 n/N_w (%)	Placebo N=898 n/N_w (%)
<60	1/862 (0.1)	0/863 (0)	0/851 (0)
≥60	861/862 (99.9)	863/863 (100)	851/851 (100)
≥90	101/862 (11.7)	93/863 (10.8)	106/851 (12.5)
≥110	2/862 (0.2)	3/863 (0.3)	0/851 (0)
≥120	0/862 (0)	0/863 (0)	0/851 (0)

Source: advs.xpt; Software: R.
Note: Participants enrolled in sites 1281 and 1483 (including those switched to 1311) are excluded.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Overall, frequencies of AEs and maximum blood pressures were similar between the PAXLOVID and placebo groups in all three trials. Specific labeling will be added to address hypertension given post-authorization findings.

17.14.4. Dysgeusia

Narratives for severe (Grade 3) dysgeusia and higher are provided below:

- Subject (b) (6): in EPIC-SR was a 33-year-old female who received PAXLOVID. On Day 1 this individual experienced severe (Grade 3) dysgeusia and study intervention was

permanently discontinued on Day 3 in response to this event with last documented dose on Day 2. This AE was reported as resolved on Day 2.

- Subject [redacted]: in EPIC-HR was a 47-year-old male who received PAXLOVID. On Day 4 this individual experienced severe (Grade 3) dysgeusia which was reported as resolved on Day 6. No changes were made to study intervention.
- Subject [redacted]: in EPIC-PEP was a 51-year-old female in the PAXLOVID 10-day group who experienced severe (Grade 3) dysgeusia on Day 2 of study intervention and was reported resolved on Day 7.
- Subject [redacted]: in EPIC-PEP was a 38-year-old male in the PAXLOVID 5-day group who experienced severe (Grade 3) dysgeusia on Day 1 of study intervention. This was reported resolved on Day 6.

18. Clinical Virology

18.1. SARS-CoV-2 RNA Shedding and Rebound

18.1.1. Methods for Analyses of Viral RNA Shedding and Serology Testing

Nasopharyngeal (NP) swab samples (in some cases [~5%] collected as nasal mid-turbinate swab samples) for viral shedding and nucleotide sequencing analyses were collected at Baseline (Day 1), Day 3, Day 5 (End-of-Treatment), Day 10 and Day 14; a small number of subjects had additional unplanned samples collected after Day 14. Viral RNA levels were measured at a central laboratory [redacted] using the Abbott RealTime Quantitative SARS-CoV-2 assay, which is a quantitative real-time RT-PCR assay. The assay targets the viral RNA-dependent RNA polymerase (RdRp, i.e., nsp12) and nucleocapsid (N) genes, and utilizes the reagents and equivalent application specifications of the Abbott Real-Time SARS-CoV-2 Qualitative assay that is available under EUA (Abbott 2021). The assay has a lower limit of quantification (LLOQ) of 100 (2 $\log_{10}$) copies/mL. The limit of detection (LOD) of the assay, based on the ≥95% positive detection rate, is also considered to be 100 (2 $\log_{10}$) copies/mL. These and other assay performance parameters were validated at the [redacted] central laboratory [redacted] For quantitative viral RNA analysis purposes, results of SARS-CoV-2 RNA "<LLOQ/Detected" were assigned a quantitative value of 1.7 $\log_{10}$ copies/mL, while results of "Not Detected" were assigned a quantitative value of 0 $\log_{10}$ copies/mL.

Serology testing involved Elecsys® Anti-SARS-CoV-2 assays targeting the spike (S) or nucleocapsid (N) proteins. Both assays detected total antibody without distinguishing between IgG, IgM, and IgA. Participants were considered to be SARS-CoV-2 seropositive at baseline if they had evidence of antibodies to either the viral S or the viral N antigen.

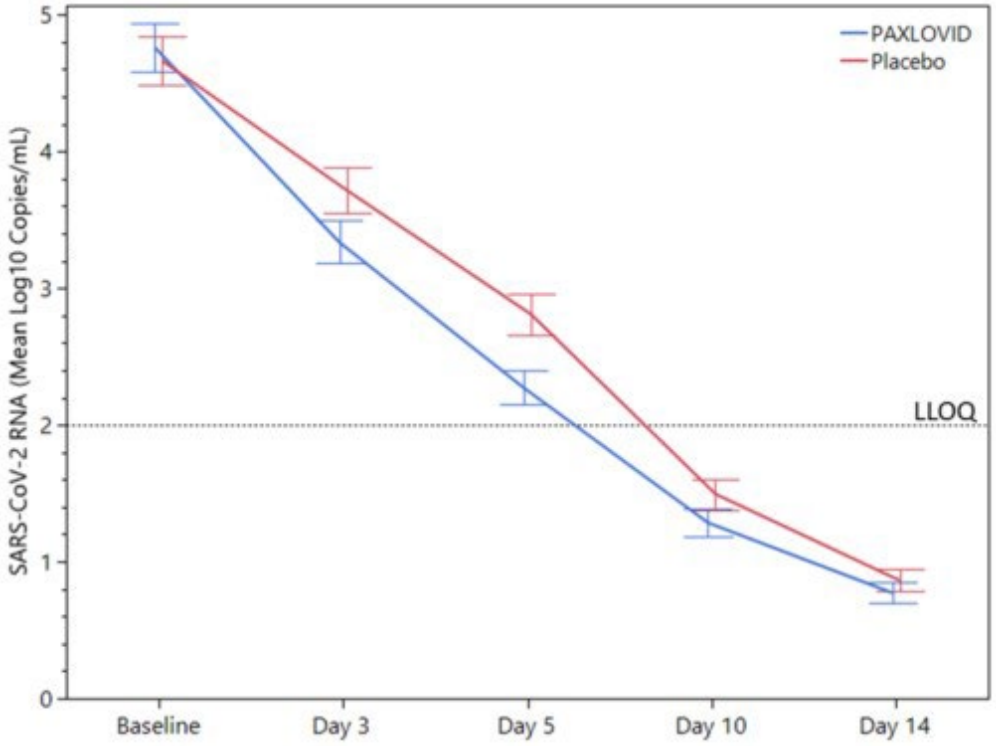
18.1.2. Effect of PAXLOVID Treatment on SARS-CoV-2 RNA Shedding

EPIC-HR

Analyses of SARS-CoV-2 RNA levels in NP samples in EPIC-HR are summarized in Figure 73. PAXLOVID treatment was associated with a mean 0.70 $\log_{10}$ copies/mL (median 0.97 $\log_{10}$ copies/mL) more rapid decline relative to placebo through Day 5/end-of-treatment. Similar results were observed in the mITT analysis (mean 0.71 $\log_{10}$ copies/mL, median 0.90 $\log_{10}$ copies/mL greater decline) and mITT1 (mean 0.68 $\log_{10}$ copies/mL, median 0.86 $\log_{10}$ copies/mL greater decline) analysis sets. Note that the Applicant's analyses of these data primarily focused on the mITT1 population and excluded subjects with a 'Not Detected' or a missing baseline viral RNA result, or subjects with non-validated/non-NP swab use. Based on these analysis parameters for the mITT1 population, PAXLOVID was associated with a mean 0.85 $\log_{10}$ copies/mL (median 0.83 $\log_{10}$ copies/mL) more rapid decline in viral RNA levels relative to placebo through Day 5/end-of-treatment.

Reference ID: 5179402

Figure 73. EPIC-HR: Analysis of SARS-CoV-2 RNA levels (Log_{10} Copies/mL) in NP Samples

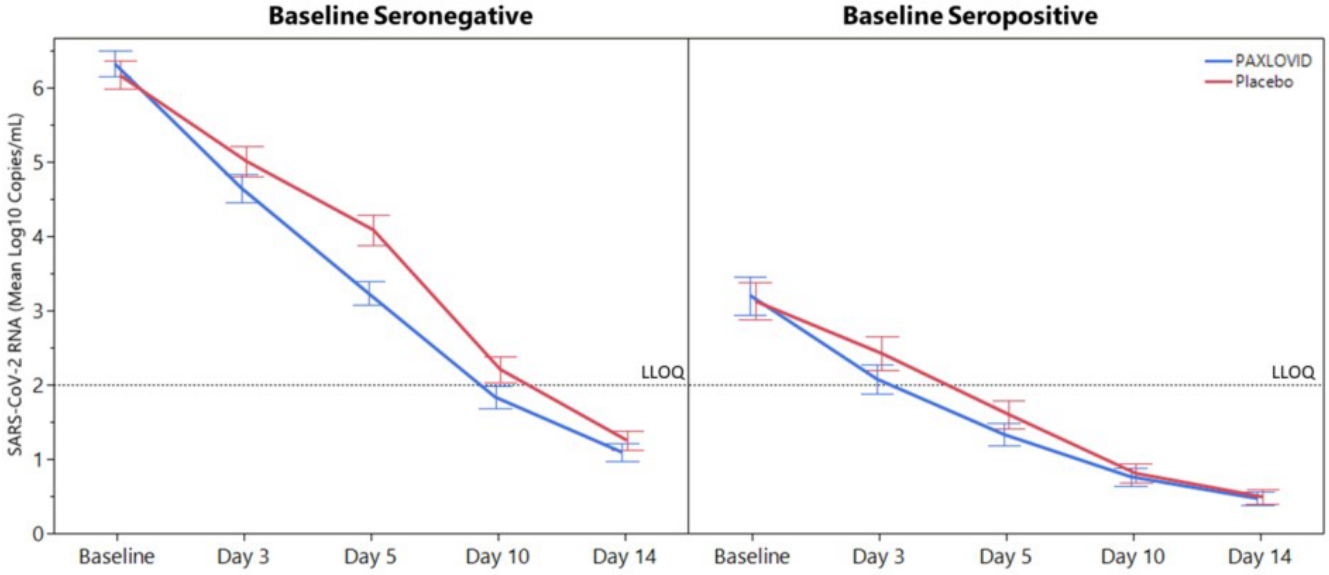


Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.48	-1.79
% (n/N) <LLOQ	47.8% (447/936)	44.1% (415/942)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT2 analysis set, i.e., all subjects who took at least one dose of study intervention.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Although viral RNA levels in NP samples at baseline were orders of magnitude lower among subjects who were baseline anti-SARS-CoV-2 seropositive, modest antiviral activity of PAXLOVID could be observed both in subjects who were baseline seronegative or baseline seropositive (Figure 74).

Figure 74. EPIC-HR: Analysis of SARS-CoV-2 RNA levels (Log_{10} Copies/mL) in NP Samples According to Baseline Serostatus



	PAXLOVID	Placebo
Day 5 Mean Change from BL (log_{10} cp/mL)	-3.13	-2.06
Day 5 % (n/N) <LLOQ	24.0% (103/429)	20.0% (87/435)

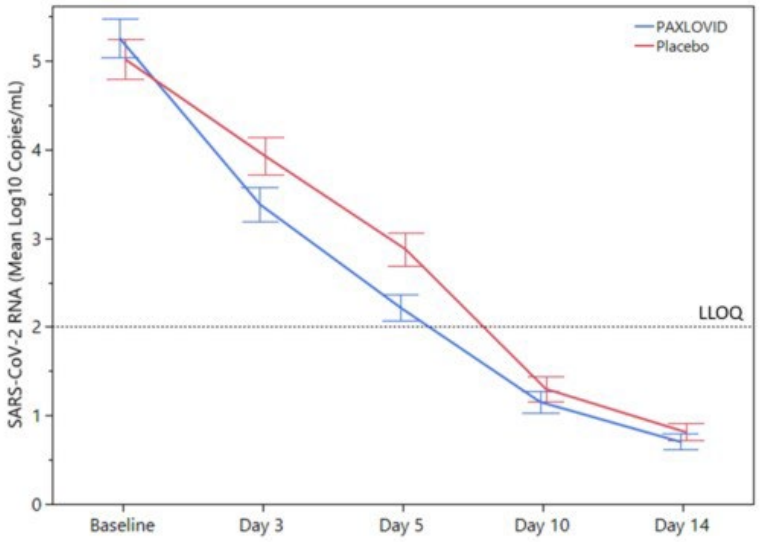
	PAXLOVID	Placebo
Day 3 Mean Change from BL (log_{10} cp/mL)	-1.11	-0.72
Day 3 % (n/N) <LLOQ	57.6% (266/462)	53.5% (242/452)
Day 5 % (n/N) <LLOQ	70.4% (311/442)	67.7% (296/437)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set, i.e., subjects who did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

EPIC-SR

Analyses of SARS-CoV-2 RNA levels in NP samples are summarized in Figure 75. PAXLOVID treatment was associated with a mean 0.87 log_{10} copies/mL (median 1.11 log_{10} copies/mL) more rapid decline relative to placebo through Day 5/End-of-Treatment. As noted above for EPIC-HR, the Applicant's analyses of these data excluded subjects with a 'Not Detected' or a missing baseline viral RNA result, or subjects with non-validated/non-NP swab use. Based on these analysis parameters for the mITT1 population, PAXLOVID was associated with a mean 0.97 log_{10} copies/mL (median 1.05 log_{10} copies/mL) more rapid decline in viral RNA levels relative to placebo through Day 5/end-of-treatment.

Figure 75. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples



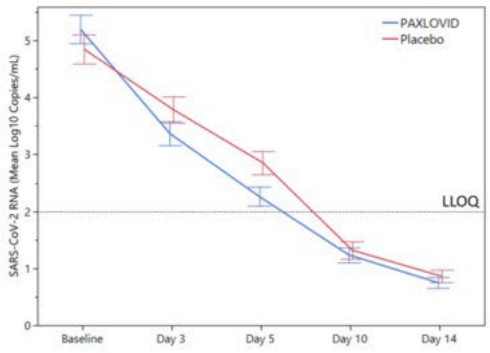
Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.03	-2.15
% (n/N) <LLOQ	50.6% (311/615)	39.8% (237/596)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set i.e., all subjects who took at least one dose of study intervention.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Antiviral activity of PAXLOVID was observed in both the 2021/Pre-Omicron and 2022/Omicron enrollment periods based on viral RNA shedding levels in NP samples (Figure 76).

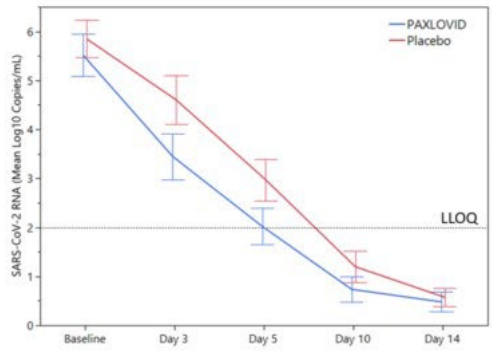
Figure 76. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples, Pre- and Post-Omicron

2021: Pre-Omicron Period (n=539 PAXLOVID, n=528 Placebo)



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-2.93	-2.01
% (n/N) <LLOQ	49.3% (251/509)	40.4% (199/492)

2022: Omicron Period* (n=114 PAXLOVID, n=106 Placebo)

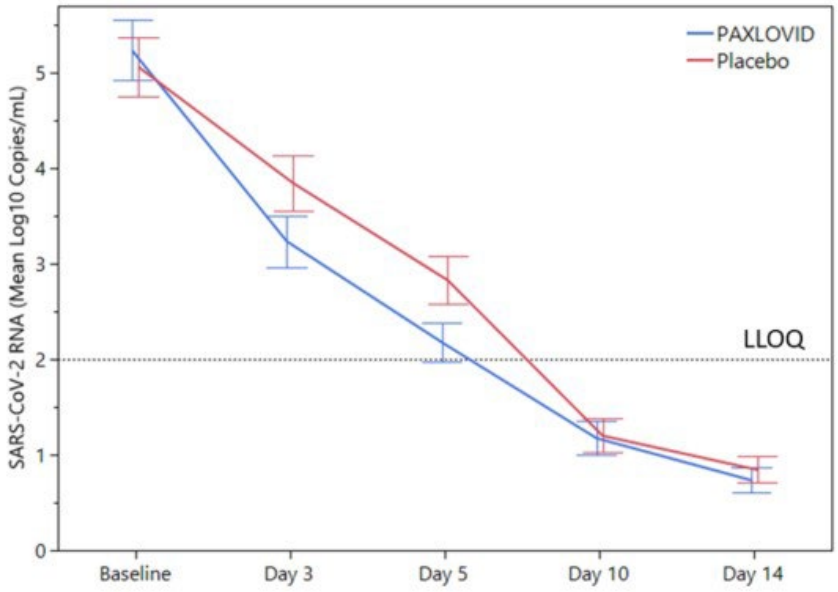


Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.52	-2.85
% (n/N) <LLOQ	56.6% (60/106)	36.5% (38/104)

Source: FDA analysis of ADMC and ADSL datasets.
Note: Charts show mean +/- 95% confidence intervals.
Note: mITT1 analysis set i.e., all subjects who took at least one dose of study intervention
* Subjects enrolled in 2022 (March-June): Omicron variants detected in >99% (143/144) of subjects w/variant data
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Antiviral activity of PAXLOVID was also observed among high-risk subjects who were enrolled in the EPIC-SR 2021 (Pre-Omicron) period and had previously received a SARS-CoV-2 vaccine (which was exclusionary in EPIC-HR) (Figure 77). Note that high-risk subjects were excluded from the 2022 enrollment period, regardless of vaccination status.

Figure 77. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} copies/mL) in NP Samples From High-Risk Subjects Who Had Received a SARS-CoV-2 Vaccine



Day 5/EOT Analysis Visit	PAXLOVID	Placebo
Mean Change from BL (log_{10} cp/mL)	-3.03	-2.27
% (n/N) <LLOQ	52.8% (163/309)	39.0% (114/292)

Source: FDA analysis of ADMC and ADSL datasets.
Note: mITT1 analysis set, 2021 enrollment period.
Note: Chart shows mean +/- 95% confidence intervals.
Abbreviations: BL, baseline; EOT, end of trial; LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; n, number of subjects in sample; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

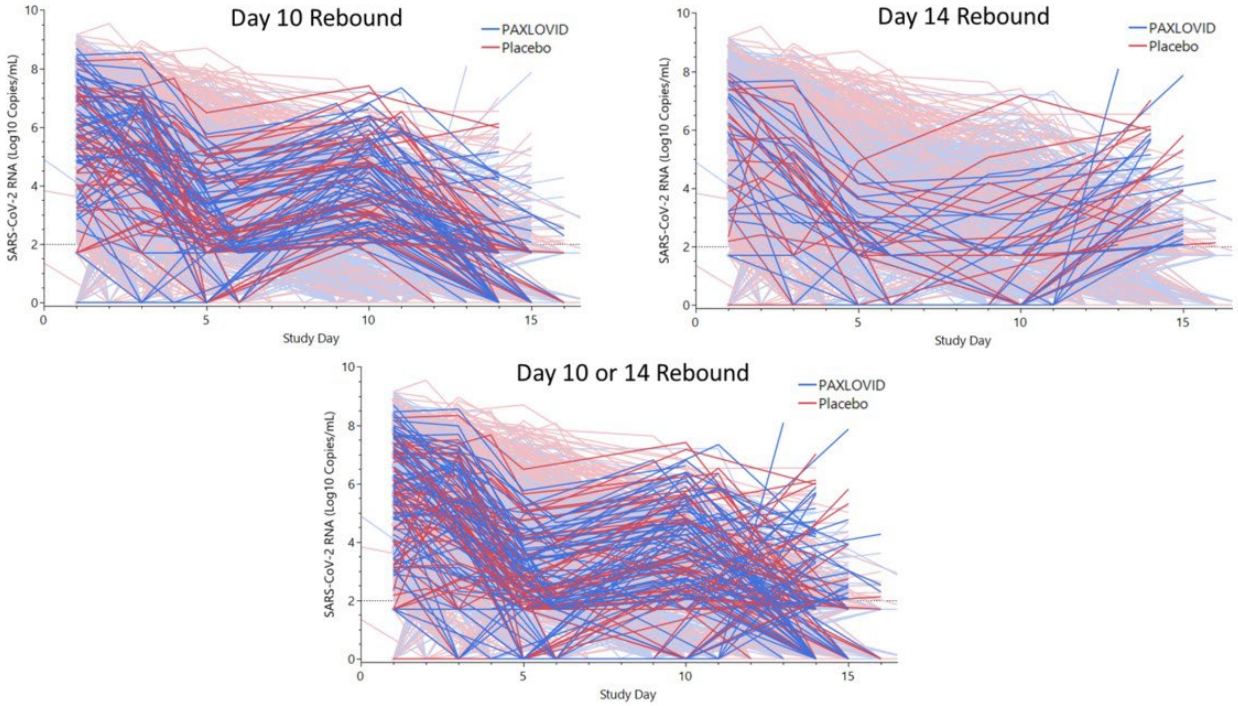
18.1.3. Additional Analyses of Viral RNA Rebound

FDA analyses of viral RNA rebound are summarized in the Integrated Review Section 6.3.6. The following section includes additional supporting analyses and details.

EPIC-HR

Viral RNA levels for individual subjects who met the definitions of viral RNA rebound are illustrated in Figure 78 and show substantial heterogeneity in the viral RNA patterns. No clear or consistent differences between PAXLOVID and placebo recipients in the RNA rebound patterns or magnitude of rebound are apparent.

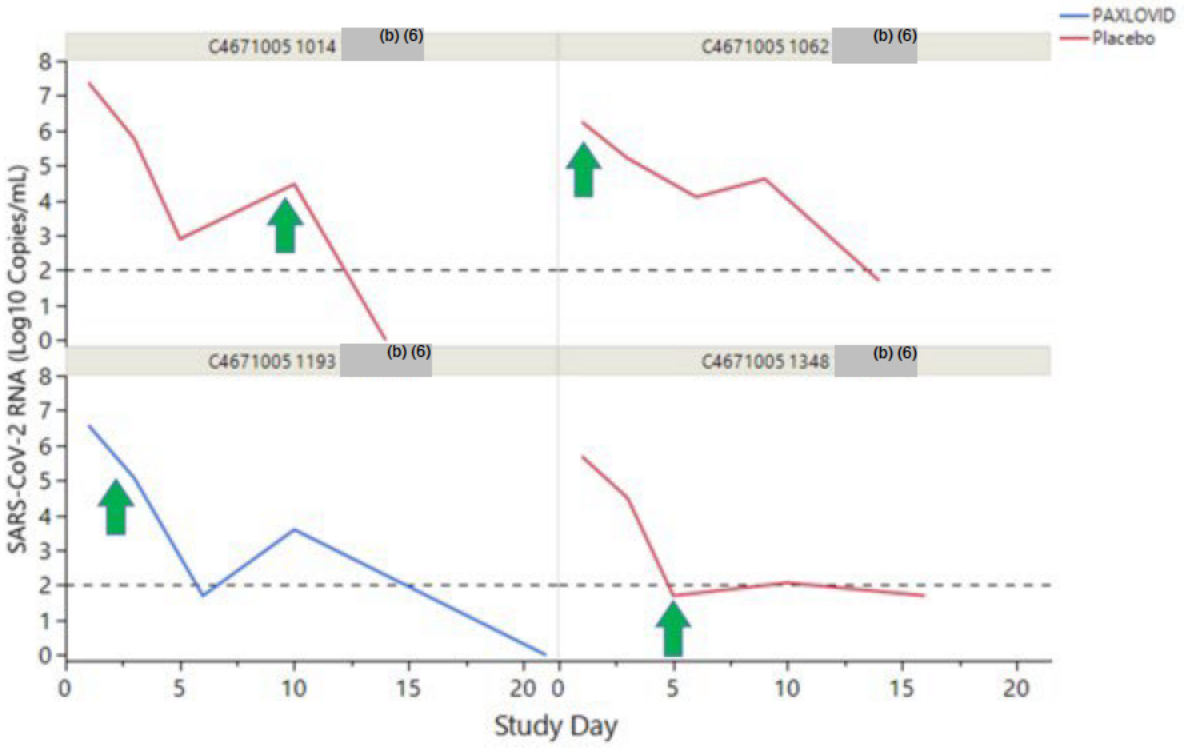
Figure 78. EPIC-HR: Viral RNA Levels Over Time for Individual Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10, Day 14, or Day 10/14 [LLOQ/0.5 Combined])



Source: FDA analysis of ADMC and ADSL datasets.
Note: Lines in the foreground indicate subjects with viral RNA rebound. Results for all other subjects are in the background.
Note: The dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Post-treatment viral RNA rebound in EPIC-HR was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28. Among the 130 subjects who experienced Day 10/14 viral RNA rebound, only 4 subjects (3%) reached the hospitalization or death endpoint (0 deaths), including 1 PAXLOVID recipient and 3 placebo recipients. Viral RNA results from these subjects are shown in Figure 79 and indicate there was not a consistent temporal relationship between post-Day 5 viral RNA rebound and the timing of hospitalization in these subjects. The hospitalization in the PAXLOVID recipient (Subject [redacted]) occurred early during treatment and the subject was discharged from the hospital on Day 8 prior to the post-treatment viral RNA rebound on Day 10. One placebo treated subject (Subject [redacted]) was admitted to the hospital on Day 9 around the time of viral RNA rebound observed on Day 10, but clearly this could not be attributed to a "post-treatment" viral RNA rebound and rather likely reflects natural COVID-19 disease progression.

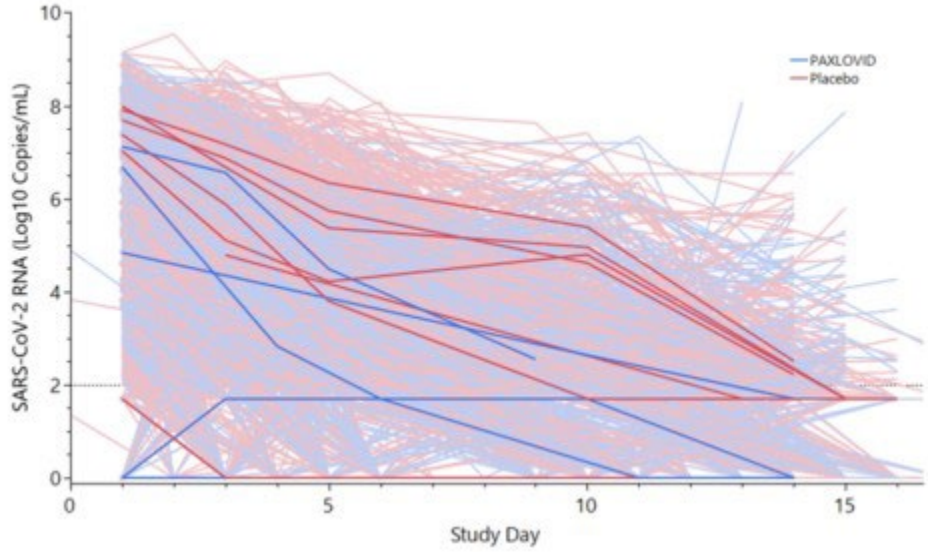
Figure 79. EPIC-HR: Viral RNA Levels in Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) and Reached the Primary Clinical Endpoint of COVID-19-Related Hospitalization or Death From Any Cause Through Day 28



Source: FDA analysis of ADMC and ADSL datasets.
Note: Arrows indicate timing of hospitalization.
Note: Dashed lines indicate the assay LLOQ.
Abbreviations: COVID-19, disease of 2019 caused by the severe acute respiratory syndrome coronavirus 2; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Post-treatment viral RNA rebound was not associated with baseline immunosuppression risk, although this was a small subgroup of subjects in the trial (n = 6 PAXLOVID, n = 7 placebo). Viral RNA results for the 13 subjects with baseline immunosuppression are shown in Figure 80. Only one of these subjects experienced post-treatment viral RNA rebound, and the subject received placebo. None of the subjects experienced the clinical endpoint of hospitalization or death. One additional subject not flagged for immunosuppression risk had HIV-1 infection, was treated with placebo, and did not have post-treatment viral RNA rebound.

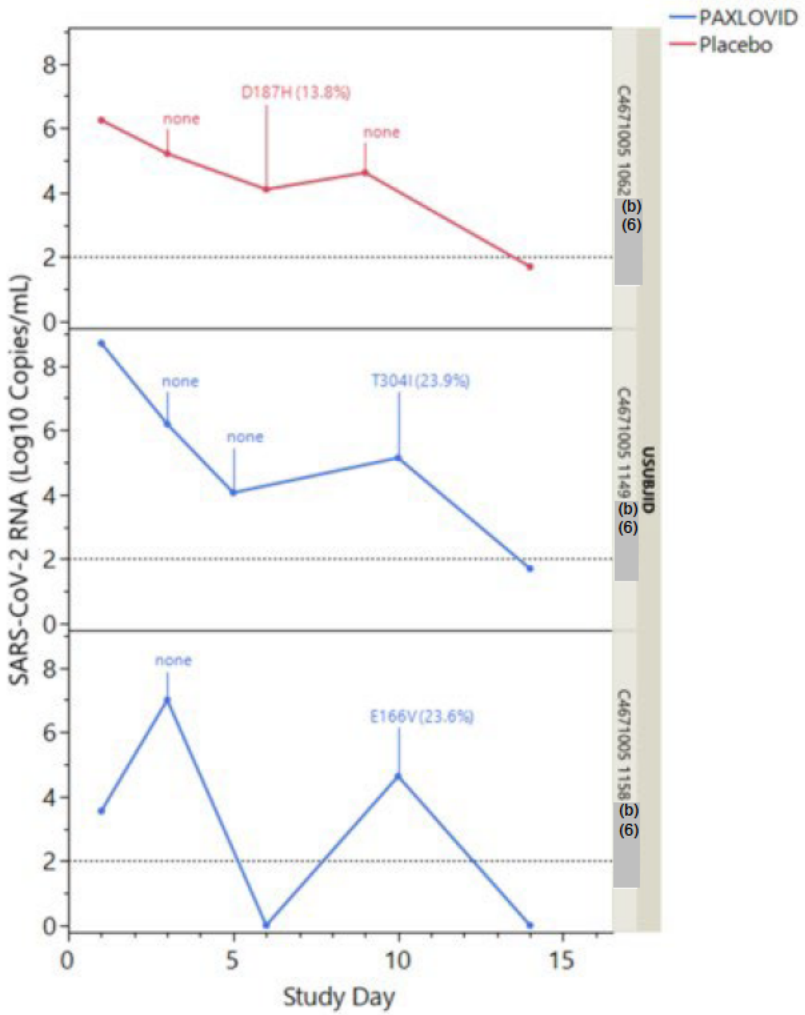
Figure 80. EPIC-HR: Viral RNA Levels in Subjects With Baseline Immunosuppression Risk



Source: FDA analysis of ADMC and ADSL datasets.
Note: Dashed line indicates assay LLOQ.
Note: Lines in the foreground indicate subjects with baseline immunosuppression risk. Results for all other subjects are in the background.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

With the exception of two PAXLOVID-treated subjects, post-treatment viral RNA rebound generally was not associated with the emergence of potential nirmatrelvir resistance-associated substitutions, defined as amino acid changes in M^{pro} at (1) a nirmatrelvir contact binding site residue (excluding positions V186 and Q189, discussed in Section 5), or (2) a position associated with resistance in cell culture. Of the 59 PAXLOVID treated subjects with viral RNA rebound and available viral sequence data, viruses from 2 (3%) subjects had a treatment-emergent substitution (TES) potentially associated with nirmatrelvir resistance, both around the time of viral RNA rebound on Day 10 (Figure 81). Virus from one placebo recipient (2% of 43 subjects with sequencing data) had an M^{pro} D187H TES, which occurred at a nirmatrelvir contact position but clearly would not have emerged due to nirmatrelvir drug pressure. Subject (b) (6) is the clearest case of post-treatment viral RNA rebound being associated with nirmatrelvir resistance, as the E166V substitution has been the clearest nirmatrelvir resistance-associated substitution observed to date based on the totality of nonclinical and clinical resistance data. The second PAXLOVID-treated subject ((b) (6)) had treatment-emergent M^{pro} T304I, which overlaps with the nsp5/nsp6 cleavage site and has also been associated with nirmatrelvir resistance in cell culture. Note that ~80% of the 103 subjects with post-treatment viral RNA rebound and viral sequencing data had sequence data available at a post-Day 5 timepoint.

Figure 81. EPIC-HR: Individual Subjects With Viral RNA Rebound and Detection of M^{pro} Treatment-Emergent Substitutions Potentially Associated With Nirmatrelvir Resistance (10% NGS Assay Sensitivity Cutoff)

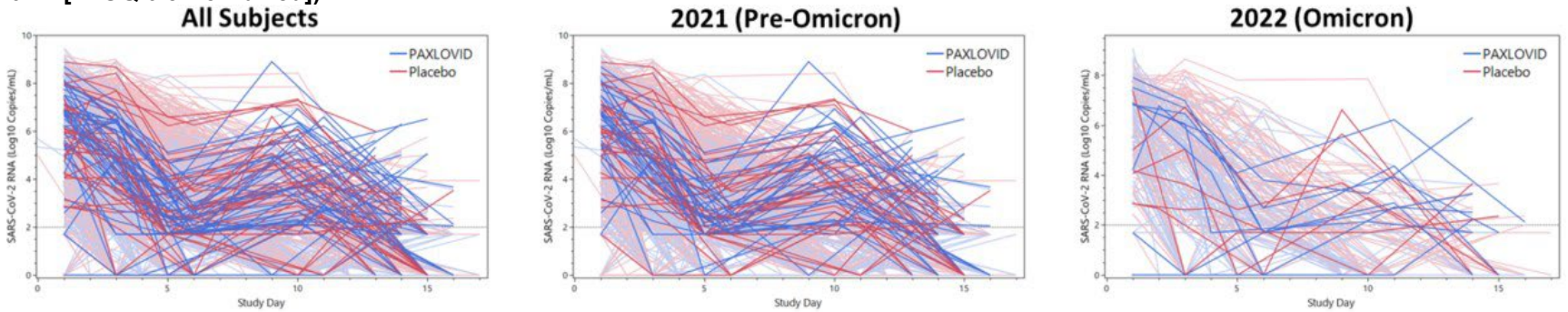


Source: FDA analysis of ADMC and ADSL datasets, and NGS analysis dataset.
Note: "None" indicates no treatment-emergent, resistance-associated substitutions were detected at the timepoint.
Note: Dashed lines indicate assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; M^{pro}, main protease; NGS, next-generation sequencing; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

EPIC-SR

Analyses of viral RNA levels for individual subjects in EPIC-SR with post-treatment viral RNA rebound again showed no obvious differences in the patterns or magnitude of viral RNA rebound between PAXLOVID and placebo recipients, either overall or within the 2021/Pre-Omicron or 2022/Omicron enrollment periods (Figure 82).

Figure 82. EPIC-SR: Viral RNA Levels Over Time for Individual Subjects Who Experienced Post-Treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined])



Source: FDA analysis of ADMC and ADSL datasets.
Note: Lines in the foreground indicate subjects with viral RNA rebound. Results for all other subjects are in the background.
Note: The dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; RNA, r bonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Consistent with the results from EPIC-HR, PAXLOVID treatment ultimately did not result in a delay in viral RNA levels reaching <LLOQ in EPIC-SR. At all analysis visits, and in both the 2021/Pre-Omicron and 2022/Omicron periods, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ (Table 187). Again, as in EPIC-HR, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely for a PAXLOVID treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 187. EPIC-SR: Proportions of PAXLOVID or Placebo Recipients With Viral RNA <LLOQ at Each Analysis Visit

	All Subjects		2021 (Pre-Omicron)		2022 (Omicron)	
Visit	**PAXLOVID**	**Placebo**	**PAXLOVID**	**Placebo**	**PAXLOVID**	**Placebo**
Day 3	31.7% (199/628)	28.3% (174/614)	31.5% (164/520)	30.3% (154/509)	32.4% (35/108)	19.1% (20/105)
Day 5/EOT	50.6% (311/615)	39.8% (237/596)	49.3% (251/509)	40.4% (199/492)	56.6% (60/106)	36.5% (38/104)
Day 10	78.9% (471/597)	73.1% (431/590)	77.3% (382/494)	72.1% (352/488)	86.4% (89/103)	77.5% (79/102)
Day 14	89.7% (555/619)	86.5% (519/600)	89.2% (456/511)	85.7% (425/496)	91.7% (99/108)	90.4% (94/104)

Source: FDA analysis of ADMC and ADSL datasets.
Abbreviations: EOT, end of trial; LLOQ, lower limit of quantitation; RNA, ribonucleic acid

On-Treatment Viral RNA Rebound (EPIC-HR)

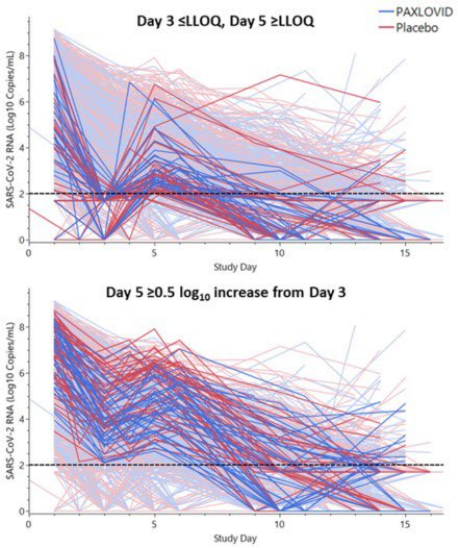
When conducting these analyses of viral RNA rebound it was observed that, while viral RNA levels in NP samples *on average* decline at a steady rate over time, and more rapidly among PAXLOVID recipients compared to placebo recipients, RNA levels from individual subjects can be highly variable and do not always follow a simple or consistent pattern, regardless of treatment. Transient increases in viral RNA levels within individuals may reflect natural variability in virus production in the upper respiratory compartment, periods of increased immune-mediated shedding of virus or viral components, or variability in technical sampling via topical swab, and not necessarily a clinically meaningful change in viral replication or viral burden due to removal of antiviral drug pressure.

To illustrate this point, viral RNA "rebound" (i.e., decrease followed by increase in RNA level) based on the same analysis parameters described above was frequently observed in EPIC-HR *during* treatment between Day 3 and Day 5 in both PAXLOVID and placebo recipients, and at a rate that was even greater than the rates of viral RNA rebound observed post-treatment (Figure 83). Given that viral RNA "rebound" observed during PAXLOVID treatment cannot be attributed to the cessation of PAXLOVID drug pressure, one should also not assume that an observation of post-treatment viral rebound must be caused by a sub-optimal treatment duration and the removal of PAXLOVID drug pressure, reflecting a post-treatment "relapse" of the viral infection. It may just as likely reflect natural variability in viral shedding or technical variability in viral sampling in the upper respiratory tract, which would be consistent with the similar rates of viral RNA rebound observed following treatment with either PAXLOVID or placebo in the EPIC-HR and EPIC-SR trials.

Figure 83. EPIC-HR: Observations of On-Treatment Viral RNA "Rebound" Between Day 3 and Day 5

	PAXLOVID	Placebo
On-treatment Viral RNA "Rebound"*	11.3% (77/680)	12.5% (74/594)
Post-treatment (D10/D14) Viral RNA Rebound, Day 5 Responders	8.1% (69/849)	6.5% (50/772)

*Day 3 Viral RNA Response (<LLOQ or ≥1 $\log_{10}$ copies/mL from BL to Day 3) AND
- Day 3 ≤LLOQ, followed by Day 5 ≥LLOQ, OR
- Day 3 ≥LLOQ, followed by Day 5 ≥0.5 $\log_{10}$ increase from Day 3



Source: FDA analysis of ADMC and ADSL datasets.
Abbreviations: D, day; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

18.2. Analyses of Cell Culture Infectious Virus in EPIC-HR

Late in the review cycle, the Applicant provided a final report on SARS-CoV-2 cell culture infectivity results from the EPIC-HR trial (Pfizer 2022b); no infectivity results were reported for EPIC-SR. A dataset with these results was subsequently submitted, but independent analyses of the dataset were not conducted.

Cell Culture Infectivity Assay Methods and Selection of Samples for Analysis

Viral infectivity assay methods were described in an earlier interim report (Pfizer 2022n). Briefly, NP/nasal swab samples were submitted for infectivity analysis if viral RNA levels were >2.0 $\log_{10}$ copies/mL. Two infectivity assays were conducted in parallel: a viral recovery assay and a viral titration (50% tissue culture infectious dose, $TCID_{50}$) immunoassay. In the viral recovery assay, samples were diluted (1:4, 1:10, 1:100 and 1:1,000) and plated onto Vero-TMPRSS2 cells. Infections were carried out for 5 days and wells positive for virus infectivity were identified by scoring for cytopathic effect (CPE). The viral titration immunoassay was also performed using Vero-TMPRSS2 cells. Samples were serially diluted and plated onto cells, and after 40 to 46 hours of incubation, the cell monolayer was fixed and assessed for the presence of SARS-CoV-2 antigen (specific antigen not specified) by an *in situ* enzyme linked immunosorbent assay (ELISA). Wells identified as positive for viral antigen were used to calculate viral titers (expressed as $TCID_{50}$/mL) of NP/nasal samples using the Spearman-Karber equation. The LLOQ of the viral titration assay was reported as 1.83 $\log_{10}$ $TCID_{50}$/mL.

Specific subjects/samples selected for infectivity analyses included the following:

1. Subjects who experienced treatment failure, defined as those who reached the primary endpoint event of COVID-19 related hospitalization or death from any cause through Day 28
2. Subjects who experienced Applicant-defined "transient viral load rebound (tVLR) or non-transient viral load rebound (ntVLR)" (note: we would refer to these as measures of "viral RNA shedding rebound"):
   - Transient viral load rebound (tVLR): Day 10 viral RNA ≥3.0 $\log_{10}$ copies/mL AND ≥0.5 $\log_{10}$ copies/mL relative to Day 5, AND Day 14 viral RNA <0.5 $\log_{10}$ copies/mL change relative to Day 5 or <3 $\log_{10}$ copies/mL (i.e., viral RNA rebound to ≥3.0 $\log_{10}$ copies/mL on Day 10 that does not persist through Day 14).
   - Non-transient viral load rebound (ntVLR): If Day 14 data are available, Day 14 viral RNA ≥3.0 $\log_{10}$ copies/mL and ≥0.5 $\log_{10}$ copies/mL relative to Day 5; if Day 14 data are not available, Day 10 viral RNA ≥3.0 $\log_{10}$ copies/mL AND ≥0.5 $\log_{10}$ copies/mL relative to Day 5. (i.e., viral RNA rebound to ≥3.0 $\log_{10}$ copies/mL through Day 14, or through Day 10 if Day 14 data are not available).
3. Subjects who experienced Applicant-defined "sustained viral load non-response (sNR-VL)," defined as having at least 2 viral RNA measurements at the Day 5, Day 10, and Day 14 visits, with all available results ≥4 $\log_{10}$ copies/mL
4. Randomly selected Day 3 and Day 5 samples with viral RNA measurements from 142 PAXLOVID-treated subjects and 142 placebo-treated subjects with baseline viral RNA levels ≥5 $\log_{10}$ copies/mL

Note that the Applicant's definitions of tVLR and ntVLR would not capture all subjects who met the more sensitive FDA Day 10/14 (LLOQ/0.5) definition of viral RNA rebound, although they would capture those with higher viral RNA levels (≥3 $\log_{10}$ copies/mL at Day 10 or Day 14) in whom positive infectivity is more likely to be detected. Also note that only analysis (4) from the list above excluded subjects from EPIC-HR sites 1274 and 1470 due to data reliability issues. The inclusion of these sites in the infectivity samples from subjects who experienced viral RNA rebound does not change any conclusions from these analyses, as only 3 subjects from these sites (all PAXLOVID-treated) experienced viral RNA rebound; none of these subjects had positive infectivity results by either assay on Day 10 or Day 14.

Infectivity Assay Results for Subjects With Viral RNA Rebound

Based on the Applicant's definitions, and using the denominators previously reported (Pfizer 2022n), tVLR was observed in 4.1% (40/977) and 2.5% (24/964) of PAXLOVID and placebo recipients, respectively; ntVLR was observed in 2.3% (22/977) and 1.5% (14/964) of PAXLOVID and placebo recipients, respectively; and combined tVLR or ntVLR were observed in 6.3% (62/977) and 3.9% (38/964) of PAXLOVID and placebo recipients, respectively.

Table 188 summarizes available qualitative (viral recovery) and quantitative (viral titration) cell culture infectivity results for subjects who met the combined tVLR or ntVLR definitions of viral RNA rebound. Among subjects with Applicant-defined viral RNA rebound, positive cell culture infectivity results at Day 10 or Day 14 were observed in 11.3% (7/62) of PAXLOVID-treated subjects and 5.3% (2/38) of placebo-treated subjects.

Table 188. EPIC-HR: Cell Culture Infectivity Results by Viral Recovery Assay for Subjects Who Met the Applicant's Definitions of "Transient Viral Load Rebound" or "Non-Transient Viral Load Rebound"

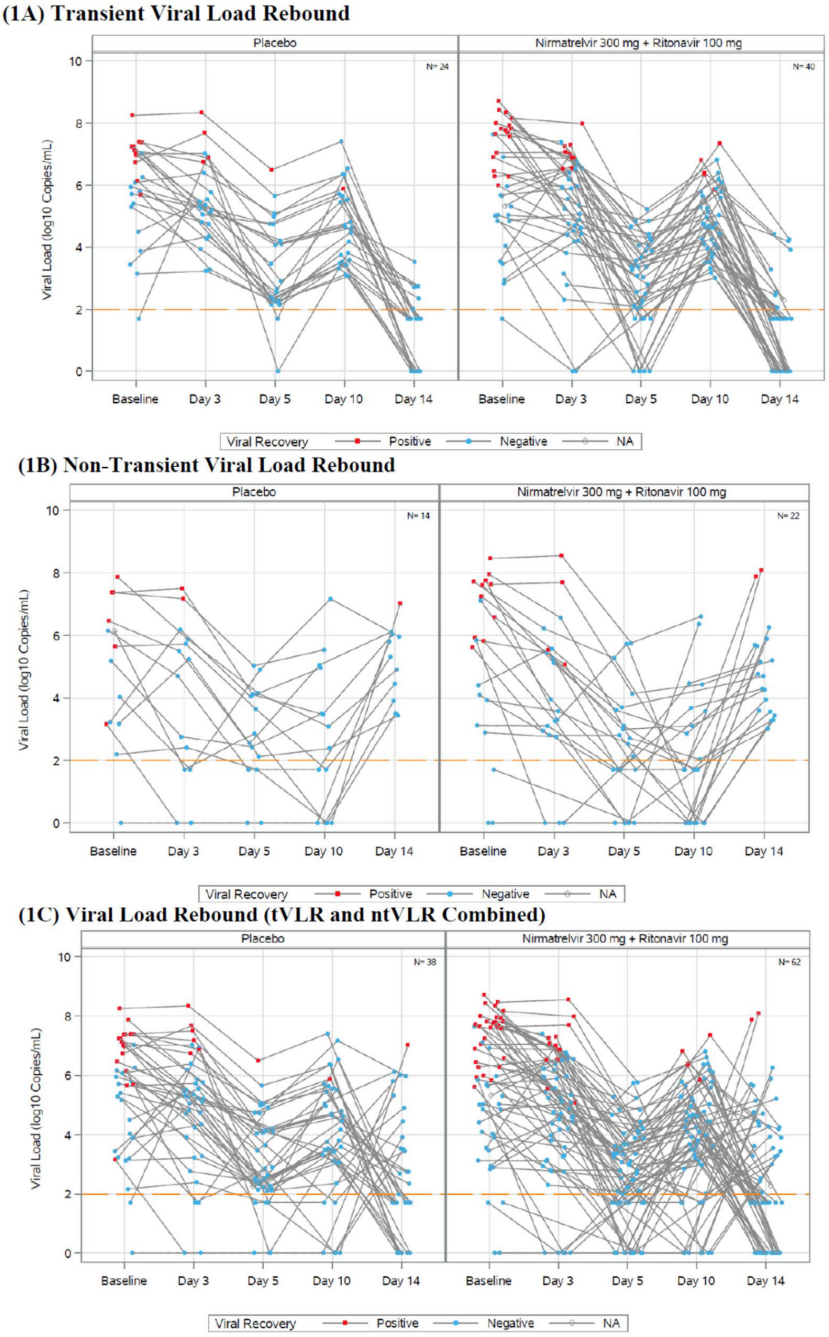
		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=62)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	29/57 (50.9%)	2.23 (2.01,2.45)	56	2	0.82	(1.53,5.17)
Day 3	13/61 (21.3%)	1.90 (1.77,2.04)	61	1.53	0.54	(1.53,3.50)
Day 5	0/62 (0.0%)	1.62 (1.57,1.67)	61	1.53	0.19	(1.53,2.17)
Day 10	5/61 (8.2%)	1.75 (1.65,1.86)	61	1.53	0.42	(1.53,3.17)
Day 14	2/59 (3.4%)	1.63 (1.57,1.68)	58	1.53	0.22	(1.53,2.50)

		Placebo (N=38)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	17/38 (44.7%)	1.93 (1.74,2.11)	37	1.83	0.55	(1.53,3.83)
Day 3	6/37 (16.2%)	1.85 (1.67,2.03)	37	1.53	0.55	(1.53,3.50)
Day 5	1/38 (2.6%)	1.70 (1.60,1.80)	38	1.53	0.30	(1.53,2.83)
Day 10	1/38 (2.6%)	1.82 (1.68,1.95)	38	1.53	0.41	(1.53,2.83)
Day 14	1/35 (2.9%)	1.69 (1.57,1.82)	35	1.53	0.37	(1.53,3.17)

Source: EPIC-HR final infectivity assay report
Abbreviations: CI, confidence interval; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; TCID50, median tissue culture infectious dose

Figure 84 shows the relationship between infectivity results and viral RNA levels. Positive infectivity results by the viral recovery assay were observed only for samples with high viral RNA levels of ≥5 $\log_{10}$ copies/mL, with the exception of a single baseline isolate that tested positive for infectivity but had a relatively lower viral RNA level of ~3 $\log_{10}$ copies/mL.

Figure 84. Viral RNA Levels for Subjects Who Experienced Applicant-Defined Viral RNA Rebound, and Association With Viral Cell Culture Infectivity by Viral Recovery Assay

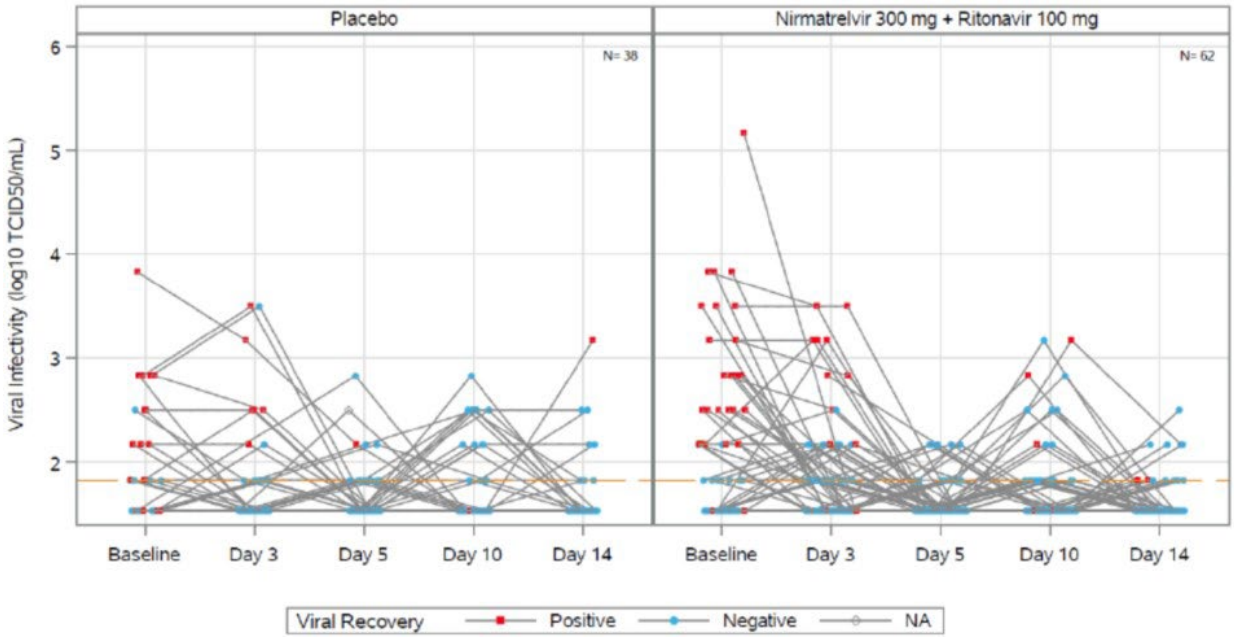


Source: EPIC-HR final infectivity assay report.
Note: Samples taking using non-validated swabs have been excluded from this analysis.
Note: The gold line LLOQ of RT-PCR assay of SARS-CoV-2 (2 $\log_{10}$ copies/mL).
Abbreviations: LLOQ; lower limit of quantitation; log, logarithm; NA, not applicable; ntVLR, nontransient viral load rebound; RNA, r bonucleic acid; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tVLR, transient viral load rebound

Quantitative infectivity results for the Day 10 and Day 14 samples based on the viral titration assay showed similar and low virus concentrations (generally ≤3 $\log_{10}$ $TCID_{50}$ units/mL) among PAXLOVID and placebo recipients with viral RNA rebound (Figure 85). Of note, several more Day 10 and Day 14 samples from both PAXLOVID and placebo recipients had qualitatively

positive infectivity results (based on ≥LLOQ) based on the viral titration assay compared to the viral recovery assay, indicating the viral titration assay is more sensitive than the virus recovery assay at detecting the presence of cell culture infectious virus.

Figure 85. Quantitative (Viral Titration Assay) Results for Subjects Who Experienced Applicant-Defined Viral RNA Rebound (tVLR and ntVLR Combined).



Source: EPIC-HR final infectivity assay report.
Note: Qualitative results by viral recovery assay are also indicated in red (positive) and blue (negative).
Note: Samples taking using non-validated swabs have been excluded from this analysis.
Note: The gold line LLOQ of $TCID_{50}$ assay (1.83 log_{10} $TCID_{50}$/mL).
Abbreviations: LLOQ; lower limit of quantitation; log, logarithm; NA, not applicable; ntVLR, nontransient viral load rebound; RNA, ribonucleic acid; $TCID_{50}$, median tissue culture infectious dose; tVLR, transient viral load rebound

Considering either the viral recovery assay or the viral titration assay, among those who experienced Applicant-defined viral RNA rebound, qualitatively positive test results for virus infectivity for Day 10 or Day 14 samples were observed for 29% (18/62) and 39% (15/38) of PAXLOVID and placebo recipients, respectively (Table 189).

Table 189. Qualitative Cell Culture Infectivity Results Based on Viral Recovery Assay or Viral Titration Assay for Subjects Who Met the Applicant's Definitions of "Transient Viral Load Rebound" or "Non-Transient Viral Load Rebound".

	Nirmatrelvir + Ritonavir (N=62)			Placebo (N=38)		
Analysis Visit	Positive by Viral Recovery	Positive by TCID50	Positive by either Viral Recovery or TCID50	Positive by Viral Recovery	Positive by TCID50	Positive by either Viral Recovery or TCID50
Day 10	5/61 (8%)	10/61 (16%)	12/61 (20%)	1/38 (3%)	11/38 (29%)	12/38 (32%)
Day 14	2/59 (3%)	5/59 (8%)	7/59 (12%)	1/35 (3%)	5/35 (14%)	5/35 (14%)
Day 10 or Day 14	7/62 (11%)	14/62 (23%)	18/62 (29%)	2/38 (5%)	14/38 (37%)	15/38 (39%)

Source: December 23, 2022 Applicant response document.
Note: All VL measurements are in log_{10} copies/mL.
Note: tVLR is defined as meeting both D10VL change from D5VL >=0.5 and D10VL >=3, and D14VL change from D5VL <0.5 or D14VL <3.
Note: ntVLR is defined as meeting one or more of the following: (1) If D14VL is available: D14VL change from D5VL >=0.5 and D14VL >=3; (2) If D14VL is not available: D10VL change from D5VL >=0.5 and D10VL >=3.
Note: Infectivity data from all subjects who experienced either tVLR or ntVLR was included.
Note: Positive by $TCID_{50}$ is defined as $log_{10}(TCID_{50})$ > LLOQ.
Abbreviations: D, day; RNA; r bonucleic acid; LLOQ; lower limit of quantitation; log, logarithm; N, total number of subjects; ntVLR, nontransient viral load; $TCID_{50}$, median tissue culture infectious dose; tVLR, transient viral load rebound; VL, viral load

In analyses of "sustained viral load non-responders (sNR-VL)," defined as those having at least 2 viral RNA measurements at the Day 5, Day 10, and Day 14 visits, with all available results ≥4 log_{10} copies/mL, there were 12 PAXLOVID treated subjects and 19 placebo subjects who met this definition. Viral infectivity qualitative results by viral recovery assay for these subjects are summarized in Table 190. PAXLOVID-treated subjects tended to have lower rates of positive infectivity at on-treatment timepoints, although similarly low infectivity rates were observed between PAXLOVID and placebo "viral load non-responders" for Days 10 and 14. Not surprisingly, quantitative $TCID_{50}$ levels trended lower among PAXLOVID-treated subjects for Day 3 and Day 5 samples.

Table 190. Infectivity Results for Subjects With "Sustained Viral Load Non-Response"

		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=12)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	8/12 (66.7%)	2.62 (2.13,3.10)	12	2.665	0.76	(1.53,3.50)
Day 3	5/12 (41.7%)	2.29 (1.79,2.79)	12	2	0.79	(1.53,3.50)
Day 5	1/10 (10.0%)	1.65 (1.54,1.76)	10	1.53	0.15	(1.53,1.83)
Day 10	3/12 (25.0%)	1.82 (1.48,2.17)	11	1.53	0.52	(1.53,3.17)
Day 14	0/9 (0.0%)	1.74 (1.47,2.02)	9	1.53	0.36	(1.53,2.50)

		Placebo (N=19)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	12/17 (70.6%)	2.78 (2.39,3.16)	17	2.83	0.75	(1.53,4.17)
Day 3	15/19 (78.9%)	2.84 (2.39,3.28)	19	2.5	0.92	(1.53,4.50)
Day 5	11/19 (57.9%)	2.13 (1.82,2.44)	19	2.17	0.64	(1.53,3.50)
Day 10	4/18 (22.2%)	1.83 (1.63,2.02)	18	1.68	0.39	(1.53,2.83)
Day 14	1/13 (7.7%)	1.82 (1.62,2.02)	13	1.83	0.33	(1.53,2.50)

Source: EPIC-HR final infectivity assay report.
Note: VL measurements are in $\log_{10}$ copies/mL
Note: sNR-VL is defined as meeting both: at least 2 VL measurements from D5, D10, and D14 visits, and VL ≥4 from all available D5/D10/D14 visits.
Abbreviations: CI, confidence interval; D, day; RNA; ribonucleic acid; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; sNR-VL, sustained viral load nonresponder; $TCID_{50}$, median tissue culture infectious dose

Among subjects who experienced treatment failure, defined as those who reached the primary endpoint event of COVID-19 related hospitalization or death for any cause through Day 28, rates of positive infectivity trended lower for PAXLOVID-treated subjects (Table 191), although the numbers of subjects for comparison with placebo-treated subjects are small due to the substantially lower rate of hospitalization or death among PAXLOVID recipients.

Table 191. Infectivity Results for Subjects With Treatment Failure

		Nirmatrelvir 300 mg + Ritonavir 100 mg (N=10)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	6/10 (60.0%)	2.18 (1.61,2.76)	10	1.85	0.80	(1.53,3.50)
Day 3	1/7 (14.3%)	1.57 (1.47,1.68)	7	1.53	0.11	(1.53,1.83)
Day 5	0/7 (0.0%)	1.66 (1.51,1.81)	7	1.53	0.16	(1.53,1.83)
Day 10	0/6 (0.0%)	1.53 (NE,NE)	5	1.53	0.00	(1.53,1.53)
Day 14	0/5 (0.0%)	1.53 (NE,NE)	5	1.53	0.00	(1.53,1.53)

		Placebo (N=68)				
		log10(TCID50)				
VISIT	Positive Infectious Status by Viral Recovery	Mean (95% CI)	n	Median	SD	Min - Max
Baseline	38/64 (59.4%)	2.27 (2.09,2.45)	64	2.17	0.72	(1.53,4.17)
Day 3	26/53 (49.1%)	2.18 (1.97,2.39)	53	1.83	0.76	(1.53,4.50)
Day 5	11/40 (27.5%)	1.88 (1.71,2.06)	40	1.53	0.55	(1.53,3.50)
Day 10	3/29 (10.3%)	1.77 (1.63,1.91)	29	1.53	0.37	(1.53,2.83)
Day 14	1/33 (3.0%)	1.58 (1.52,1.64)	33	1.53	0.16	(1.53,2.17)

Source: EPIC-HR final infectivity assay report.
Note: Treatment failure is defined as COVID-19-related hospitalization or death from any cause through D28.
Abbreviations: CI, confidence interval; D, day; RNA; ribonucleic acid; log, logarithm; Max, maximum; Min, minimum; N, number of subjects in the viral subgroup within each treatment arm; n, number of subjects with a value in the analysis category for that given visit; SD, standard deviation; sNR VL, sustained viral load nonresponder; TCID50, median tissue culture infectious dose

In the analysis of samples from randomly selected PAXLOVID recipients (n = 142) and placebo recipients (n = 142) with baseline viral RNA ≥5 $\log_{10}$ copies/mL, PAXLOVID led to a more rapid decline in cell culture infectious virus without evidence of prolonged virus shedding in the post-treatment period compared to placebo-treated subjects (Table 192). Approximately half of the subjects had positive cell culture infectivity results detected in baseline samples based on the viral titration assay. Of these subjects, those treated with PAXLOVID were more likely to have negative infectivity results on Day 3 and Day 5, while >95% of both PAXLOVID and placebo subjects had negative infectivity results on Day 10 and Day 14.

Table 192. Summary of Negative Cell Culture Infectivity Results Based on Viral Titration ($TCID_{50}$) Assay

Visit	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=75)	Placebo(N=74)	Odds Ratio	95% CI	P-Value
Day 3	56/75 (74.7%)	38/74 (51.4%)	2.79	(1.40,5.58)	0.0018
Day 5	73/75 (97.3%)	58/74 (78.4%)	10.07	(2.22,45.57)	0.0003
Day 10	68/71 (95.8%)	60/63 (95.2%)	1.13	(0.22,5.83)	0.3162
Day 14	69/70 (98.6%)	66/68 (97.1%)	2.09	(0.19,23.61)	0.3721

Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.

Source: EPIC-HR final infectivity assay report.
Note: Results are shown only for those with positive infectivity results at baseline.
Note: Participants enrolled at Sites 1274 and 1470 (including those switched to 1276) are excluded.
Abbreviations: CI, confidence interval; N, total number of subjects; TCID50, median tissue culture infectious dose

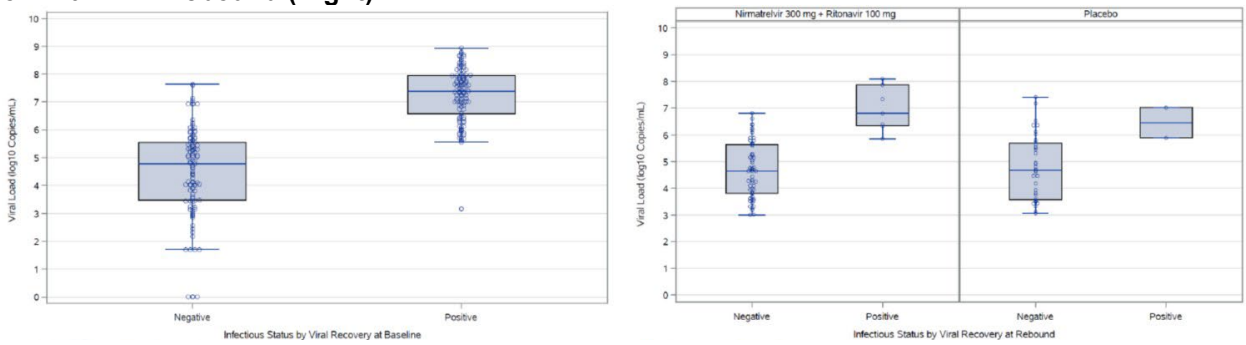
Infectivity assessments were also conducted for 3 PAXLOVID-treated subjects in whom the M^{pro} E166V substitution was detected. As noted in Section 18.3.2, this was the clearest resistance pathway observed in EPIC-HR. For two of the subjects, samples with E166V (≥90% frequency in both) tested negative for cell culture infectivity by both the virus recovery and viral titration

assays. For the third subject (SUBJID (b) (6)), E166V was detected at a 24% frequency, and the sample tested negative for virus recovery, but was positive in the viral titration assay. Given that E166V was not predominant in the viral population, it is unknown if it was represented in the cell culture infectious virus detected in this sample. Note that this subject also experienced post-treatment viral RNA rebound. Although it is challenging to draw broad conclusions given the mixed viral population and single subject observation, this raises at least the theoretical concern that in rare cases of viral rebound following PAXLOVID treatment, the virus population could be transmissible and include nirmatrelvir-resistant virus.

Of note, for the second PAXLOVID-treated subject with viral RNA rebound associated with emergence of an M^{pro} substitution potentially associated with nirmatrelvir resistance (Subject (b) (6), T304I [24%]), the Day 10 sample from this subject similarly tested negative by viral recovery but positive in the viral titration assay (FDA analysis of ADMCINF dataset).

As noted above, positive viral recovery results were usually obtained only from samples with high viral RNA levels ≥5 $\log_{10}$ copies/mL. This was observed both for baseline samples and for samples at Day 10 or 14 for those who experienced viral RNA rebound (Figure 86).

Figure 86. Boxplot of Viral RNA Levels Relative to Detection of Cell Culture Infectious Virus by Viral Recovery Assay for Samples Collected at Baseline (Left) and Samples Collected at the Time of Viral RNA Rebound (Right)



Source: EPIC-HR final infectivity assay report.
Note: Samples taken using non-validated swabs have been excluded from these analyses.
Abbreviations: log, logarithm; RNA, ribonucleic acid

Given that a viral RNA level of ≥5 $\log_{10}$ copies/mL in NP samples may indicate a greater likelihood of detection of cell culture infectious virus, an independent analysis of viral RNA results was conducted to assess the frequencies of PAXLOVID- and placebo-treated subjects with viral RNA ≥5 $\log_{10}$ copies/mL at different treatment visits. The results are shown in Table 193. Consistent with analyses of viral RNA results <LLOQ and the frequency of detection of cell culture infectious virus across all study visits, subjects treated with PAXLOVID were less likely to have viral RNA ≥5 $\log_{10}$ copies/mL at all study visits through Day 14, again confirming that PAXLOVID treatment was not associated with prolonged viral RNA shedding in NP samples, irrespective of viral RNA rebound. Furthermore, among those who experienced post-treatment viral RNA rebound, there was no apparent difference in the proportions of PAXLOVID and placebo recipients whose viral RNA rebounded to a level ≥5 $\log_{10}$ copies/mL on Day 10 or Day 14, further illustrating that the magnitude of viral RNA rebound was similar between PAXLOVID and placebo recipients.

Table 193. Frequencies of Subjects With Viral RNA ≥5 log10 Copies/mL at Each Study Visit

All Subjects		
Visit	Paxlovid (n=1035)	Placebo (n=1048)
Day 3	29.1% (282/970)	38.9% (381/980)
Day 5/EOT	10.3% (96/936)	23.9% (225/942)
Day 10	3.7% (34/922)	5.3% (48/903)
Day 14	1.0% (9/942)	1.5% (14/948)
Subjects With Viral RNA Rebound*		
Visit	Paxlovid (n=77)	Placebo (n=53)
Day 10	25.0% (19/76)	23.1% (12/52)
Day 14	9.5% (7/74)	12.2% (6/49)
Day 10 or Day 14	33.8% (26/77)	30.2% (16/53)

Source: FDA analysis of ADMC and ADSL datasets.
* Day 10/14 LLOQ/0.5 Combined Definition.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; n, number of subjects in sample

In summary, positive cell culture infectivity results from Day 10 or Day 14 samples were observed for a subset of subjects who experienced post-treatment viral RNA rebound, regardless of whether they were treated with PAXLOVID or placebo. In an analysis of samples from randomly selected PAXLOVID or placebo recipients with baseline viral RNA ≥5 $\log_{10}$ copies/mL, PAXLOVID led to a more rapid decline in cell culture infectious virus without evidence of prolonged virus shedding in the post-treatment period compared to placebo-treated subjects. For 2 PAXLOVID-treated subjects with post-treatment viral RNA rebound associated with emergence of the M^{pro} E166V or T304I substitutions, cell culture infectious virus was detected in the post-treatment rebound sample, indicating that in rare cases of viral rebound following PAXLOVID treatment the virus population could be transmissible and include nirmatrelvir-resistant virus (note: the precise relationship between SARS-CoV-2 cell culture infectivity and transmissibility is unclear).

18.3. Drug Resistance Analyses for EPIC-HR and EPIC-SR

18.3.1. Viral Sequencing Analysis Methods

NP samples were analyzed at the (b) (4) using a "tiling amplicon panel" next-generation sequencing (NGS) method based on the Illumina platform (for details see: (b) (4) The sequencing covers the whole SARS-CoV-2 genome. Samples were required to have SARS-CoV-2 RNA levels >500 copies/mL (>2.7 $\log_{10}$ copies/mL) for analysis. Sequences were mapped against the SARS-CoV-2 Wuhan-Hu-1 reference sequence (NCBI 045512.2). Amino acid substitutions detected at a ≥1% frequency were reported. Independent FDA analyses were conducted starting from the Applicant's analysis-ready datasets, and additional independent analyses were conducted using the raw NGS fastq data.

Due to evidence of a large number of sequencing artifacts observed at low amino acid frequencies, initial analyses of treatment-emergent substitutions (TES) conducted by FDA and

by the Applicant, including for prior EUA submissions, used a 5% amino acid frequency cutoff for detection versus non-detection of amino acid substitutions. However, during the NDA review (and also noted in prior EUA reviews) it was observed that there were still numerous amino acid changes in the ~5 to 10% frequency range in both PAXLOVID- and placebo-treated subjects, including many changes that likely represent sequencing artifacts such as frameshifts and premature stop codons. Even after censoring frameshifts and stop codons, using a 5% frequency cutoff there were 811 M^{pro} or M^{pro} cleavage site TES detected in 45% (258/573) of subjects who received placebo, which is an unexpectedly high number of changes in a conserved protein for virus populations that are not under M^{pro} inhibitor selective pressure. Increasing the frequency cutoff from 5% to 10% eliminated 70% of these detected TES, consistent with a high rate of sequencing artifacts reported in the 5-10% frequency range.

As further evidence of a potentially high rate of amino acid sequencing artifacts at frequencies <10%, in the full table of reported amino acid substitutions throughout the SARS-CoV-2 genome using the original ≥1% cutoff, 42% (370,131/874,579) of amino acid changes were frameshifts or stop codons. Of these changes, 86% were reported in the ≥1% to <5% frequency range, and another 10% were reported in the ≥5% to <10% frequency range. Using a less sensitive 10% frequency cutoff eliminates 96% of reported frameshifts and stop codons, and presumably most sequencing artifacts of any type. Therefore, because we were concerned that a substantial proportion of TES detected only at the 5 to 10% level could reflect sequencing artifacts and underemphasize real changes occurring in the viral population, we revised our sensitivity cutoff for sequencing analyses to 10% during the review.

Independent FDA analyses of the SARS-CoV-2 sequencing data focused on the full M^{pro} amino acid coding sequence and M^{pro} cleavage sites. Table 194 summarizes the M^{pro} cleavage sites that were analyzed and their positions in the SARS-CoV-2 polyproteins (pp) pp1a and pp1ab.

Table 194. M^{pro} Cleavage Sites Analyzed for PAXLOVID Treatment-Emergent Changes

Cleavage Site	pp1a/pp1ab Proteins Cleaved	AA Cleavage Sites	pp1ab AA Positions
M^{pro} (nsp5) CS#1	nsp4/nsp5	SAVLQ↓SGFRK	3259-3268
M^{pro} (nsp5) CS#2	nsp5/nsp6	GVTFQ↓SAVKR	3565-3574
M^{pro} (nsp5) CS#3	nsp6/nsp7	VATVQ↓SKMSD	3855-3864
M^{pro} (nsp5) CS#4	nsp7/nsp8	RATLQ↓AIASE	3938-3947
M^{pro} (nsp5) CS#5	nsp8/nsp9	AVKLQ↓NNELS	4136-4145
M^{pro} (nsp5) CS#6	nsp9/nsp10	TVRLQ↓AGNAT	4249-4258
M^{pro} (nsp5) CS#7	nsp10/nsp11-12	EPMLQ↓SADAQ	4388-4397
M^{pro} (nsp5) CS#8	nsp12/nsp13	HTVLQ↓AVGAC	5320-5329
M^{pro} (nsp5) CS#9	nsp13/nsp14	VATLQ↓AENVT	5921-5930
M^{pro} (nsp5) CS#10	nsp14/nsp15	FTRLQ↓SLENV	6448-6457
M^{pro} (nsp5) CS#11	nsp15/nsp16	YPKLQ↓SSQAW	6794-6803

Source: Adapted from (Pfizer 2022a).
Abbreviations: AA, amino acid; CS, cleavage site; Mpro, main protease; nsp, nonstructural protein; pp, polyprotein

18.3.2. EPIC-HR: SARS-CoV-2 Variants and Resistance Analyses

As expected based on the timing of subject enrollment in EPIC-HR, clades/lineages representative of the SARS-CoV-2 Delta variant were predominant among subjects with available viral sequencing and variant assignment results, representing ~99% of detected variants

(Table 195). Of the 78 subjects who reached the hospitalization/death endpoint, 77 (99%) were infected with a Delta variant.

Table 195. SARS-CoV-2 Clades/Variants Detected in EPIC-HR

Nextstrain Clade/ WHO Variant	Paxlovid (n=764)	Placebo (n=757)	All Subjects (n=1521)
Any Delta Variant	752 (98%)	750 (99%)	1502 (99%)
21J/Delta	601 (79%)	622 (82%)	1223 (80%)
21I/Delta	120 (16%)	112 (15%)	232 (15%)
21A/Delta	31 (4%)	16 (2%)	47 (3%)
20J/Gamma,V3	3 (<1%)	3 (<1%)	6 (<1%)
21G/Lambda	3 (<1%)	0 (0%)	3 (<1%)
20C	1 (<1%)	2 (<1%)	3 (<1%)
20I/Alpha,V1	2 (<1%)	0 (0%)	2 (<1%)
21H/Mu	2 (<1%)	0 (0%)	2 (<1%)
20G	1 (<1%)	1 (<1%)	2 (<1%)
20A	0 (0%)	1 (0%)	1 (<1%)

Source: FDA analysis of NGS analysis dataset.
Abbreviations: n, number of subjects in sample; NGS, next-generation sequencing; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

Three different algorithms/approaches were used to identify PAXLOVID TES in EPIC-HR:

- Unbiased analysis ("TE"): Amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (any change at same position), and at a ≥2-fold greater frequency than in placebo-treated subjects, considering all available timepoints from subjects with baseline and at least one post-baseline result. Note that the Applicant's similar algorithm for identifying TES initially did not consider Day 3 results, which resulted in some substitutions identified in the FDA analyses but not reported by the Applicant.
- Any treatment-emergent amino acid changes at any of the following NIR M^{pro} contact residues (within 5 Å) ("CR"): H41, M49, Y54, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166, L167, P168, H172, V186, D187, R188, Q189, T190, A191, Q192.
- Any treatment-emergent amino acid changes at any M^{pro} residues associated with NIR phenotypic resistance in cell culture (Section 20.3, partially overlaps with contact residues) ("Ph"): T21, L50, P108, T135, F140, S144, C160, E166, L167, T169, H172, A173, V186, R188, A191, A193, P252, S301, T304.

Results from these analyses are summarized in Table 196.

Table 196. PAXLOVID Treatment-Emergent Amino Acid Substitutions Observed in EPIC-HR

AA Position and Substitution(s)	Reporting Criteria[1]	# PAX-Tx Subjects (n=539 w/ data)	# PBO-Tx Subjects (n=552 w/ data)	AA Frequency in PAX-Tx Subjects[2]	Hosp. or Death Endpt (PAX-Tx Subjects)	NIR Fold-Change (AA)[3]
M^{pro} Amino Acid Substitutions						
G11C/S/V	TE	3 (1 each)	1 (C)	0.10-0.16	N	nd
T111I	TE	3	1	0.11-0.14	N	nd
P132H/L/S	TE	5 (2H,1L,2S)	0	0.18-0.35	N	0.5-1.1[(c)] (H) 0.6-1.1[(b)] (H/L/S)
C145F/R/Y	CR	1 (F/R/Y in same subject)	0	0.41 (F/R/Y pooled)	N	nd
C160R	Ph	1	0	0.15	N	nd
E166V	TE, CR, Ph	3	0	0.24-0.94	N	25-288[(c)]
P168S	CR	1	0	0.12	N	0.6[(b)]
A173T	Ph	1	0	0.20	N	0.9-2.3[(c)] (V) <1.8[(b)] (T)-16[(b)] (V)
V186G	CR, Ph	22	15	0.10-0.24	N	1.4[(b)]
R188M	CR, Ph	1	0	0.13	N	1.0[(b)]
Q189K	CR	5	5	0.14-0.32	N	0.2[(c)] <1.6[(b)]
T190I	CR	1	1	0.29 (0.33 in PBO)	N	0.7[(b)]
A193P	Ph	1	0	0.13	N	0.9[(b)]
A260S/T/V	TE	7 (1S,4T,2V)	1 (V)	0.11-0.21	Yes=1, N=6	0.6[(b)] (V)
T304I	Ph	1	0	0.24	N	2.1-5.5[(c)] 1.0[(b)]
Any	TE, CR or Ph	53 (10%)	28 (5%)			
Any	CR or Ph	37 (7%)	25 (5%)			
M^{pro} Cleavage Site Amino Acid Substitutions						
CS#2 A3571V	TE	3	1	1 (all >0.99)	N	nd
CS#8 A5328P/S	TE	4 (3S,1P)	0	0.10-0.34	N	nd

Source: FDA analysis of NGS analysis dataset.

[1] Substitutions detected in PAXLOVID-treated subjects meeting one or more of the following criteria:

- TE: treatment-emergent in ≥3 PAXLOVID-treated subjects (i.e., ≥0.5% of subjects) at the same amino acid position in M^{pro} or M^{pro} cleavage site, AND ≥2-fold more frequently in PAXLOVID-treated subjects relative to placebo-treated subjects
- CR: emerged in ≥1 PAXLOVID-treated subject at a nirmatrelvir contact residue in M^{pro} (w/in 5 Å); 'Any' calculations included substitutions only detected in Placebo-treated subjects.
- Ph: emerged in ≥1 PAXLOVID-treated subject at a residue in M^{pro} associated with NIR phenotypic resistance in cell culture (i.e., emerged in selection studies and/or shown to confer reduced NIR activity in cell culture); 'Any' calculations included substitutions only detected in Placebo-treated subjects)

[2] Amino acid frequency ≥10% considered for detection.

[3] Based on EC_{50} value in cell culture assay:

- [(c)] or IC_{50} value in biochemical assay
- [(b)]. nd, no data

Abbreviations: AA, amino acid; C, cysteine; CS, cleavage site; EC_{50}, half-maximal effective concentration; Endpt, endpoint; F, phenylalanine; H, histidine; Hosp, hospitalization; IC_{50}, half-maximal inhibitory concentration; L, leucine; M^{pro}, main protease; N, no; n, number of subjects in sample; nd, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; P, proline; PAX, paxlovid; PBO, placebo; R, arginine; S, serine; T, threonine; Tx, treated; V, valine; w/, with; Y, tyrosine

Key observations from these analyses include the following:

- Overall, the detection of PAXLOVID treatment-emergent viral populations potentially resistant to nirmatrelvir was uncommon. Considering nirmatrelvir contact residues ("CR" positions) and positions shown to be associated with phenotypic resistance in cell culture ("Ph" positions), 37 (7%) PAXLOVID recipients and 25 (5%) placebo recipients had a TES detected at one of these positions, indicating a generally modest signal of potential resistance emergence associated with PAXLOVID treatment. Considering the full list of M^{pro} substitutions noted in Table 196, including TES observed at positions of unknown significance, at least one of the noted M^{pro} amino acid substitutions was detected in 53 (10%) PAXLOVID recipients, of whom 50 (94%) had only a single M^{pro} TES detected (including mixtures at the same position) while 3 other PAXLOVID recipients had 2 different M^{pro} substitutions detected, with no shared combinations between the 3 subjects.
- Considering all of the TES noted in these analyses, the primary endpoint of hospitalization or death was observed in only 1 PAXLOVID-treated subject (SUBJID (b) (6); hospitalization) with one of these substitutions detected, M^{pro} A260T (A260 substitutions discussed further below).
- M^{pro} E166V was the clearest nirmatrelvir resistance-associated TES observed. Although treatment-emergent E166V was detected only in 3 (0.6%) PAXLOVID treated subjects, in 2 of the subjects the substitution was detected in ≥90% of sequence reads at this position on Day 5. It also did not emerge in any placebo recipients. As summarized in Section 20, M^{pro} E166 is located in the nirmatrelvir binding site, and a variety of substitutions at this position have been shown by the Applicant and other independent researchers to be associated with resistance to nirmatrelvir in cell culture and biochemical assays. In recombinant SARS-CoV-2 viruses, the M^{pro} E166V substitution conferred 25 to 288-fold higher nirmatrelvir EC_{50} values (Zhou et al. 2022b; Iketani et al. 2023).
- M^{pro} V186G, which is in the nirmatrelvir binding site (no direct interaction), was a commonly detected TES in both PAXLOVID and placebo treated subjects. This may represent a common sequencing artifact in the Applicant's analysis, as it was frequently detected in both treatment arms and only one PAXLOVID-treated subject was found to have a TES at this position (V186L) in independent FDA analyses of the raw NGS data (using a 10% frequency threshold, see Section 18.3.4). Furthermore, V186G had no impact on nirmatrelvir activity in a biochemical assay. Thus, the totality of data indicate that V186G was not a clear nirmatrelvir resistance-associated substitution in EPIC-HR.
- Like M^{pro} V186G, Q189K is in the nirmatrelvir binding site (no direct interaction) and was detected in numerous subjects in baseline and post-baseline samples, with no clear signal of treatment emergence associated with PAXLOVID over placebo. Position Q189 is highly conserved in publicly available SARS-CoV-2 sequence data, and previous analyses found a high likelihood of sequence artifacts reported at this position (as indicated by low coverage and bias in the read direction balance). Furthermore, independent FDA analyses of the raw NGS data did not identify Q189K in any PAXLOVID or placebo treated subjects at any visit (using a 10% frequency threshold, see Section 18.3.4). The Applicant had previously reported that Q189K confers reduced nirmatrelvir activity in a biochemical assay; however, it was subsequently found that the reduction observed was an artifact of the negative impact of the substitution on M^{pro} catalytic efficiency. Also, Q189K engineered into SARS-CoV-2 did

not reduce nirmatrelvir activity in cell culture. Therefore, the totality of data indicate Q189K was not a clear nirmatrelvir resistance-associated substitution in EPIC-HR.

- The M^{pro} T304I substitution emerged in one PAXLOVID-treated subject. T304 is located near the C-terminus of M^{pro} and overlaps the P3 position of the nsp5/nsp6 cleavage site. In cell culture assays, the presence of T304I in SARS-CoV-2 was associated with a 2.1 to 5.5-fold increase in nirmatrelvir EC_{50} values, while it had no impact on nirmatrelvir activity in biochemical assays when engineered into recombinant SARS-CoV-2 M^{pro} enzyme. These findings raise the possibility that any contribution of T304I to nirmatrelvir resistance is related to its impact on the nsp5/nsp6 cleavage site (see also Section 20).
- PAXLOVID TES were infrequently observed at other M^{pro} nirmatrelvir contact positions or other positions associated with nirmatrelvir resistance in nonclinical studies, including C145F/R/Y (n = 1), P168S (n = 1), A173T (n = 1), R188M (n = 1), T190I (n = 1; also detected in 1 placebo recipient), and A193P (n = 1). The significance of treatment-emergent C145F/R/Y and its role in nirmatrelvir resistance is unclear as C145 is a critical catalytic residue in the M^{pro} active site and amino acid changes at this position rendered the enzyme inactive in biochemical assays.
- Substitutions at M^{pro} position A260 (A260S/T/V), which is outside of the nirmatrelvir binding site and not known to be a nirmatrelvir resistance-associated position, appeared to be enriched in PAXLOVID recipients (n = 7) compared to placebo recipients (n = 1). Only A260T emerged in one PAXLOVID treated subject in independent FDA analyses of the raw NGS data using a 10% frequency threshold (see Section 18.3.4). The A260S, T or V substitutions did not reduce nirmatrelvir activity in a biochemical assay. Of note, in EPIC-SR, A260P/V emerged in 4 placebo recipients and 0 PAXLOVID recipients. Thus, A260 substitutions are considered unlikely to be associated with nirmatrelvir resistance.
- Substitutions P132H/L/S emerged in 5 PAXLOVID-treated subjects and 0 placebo-treated subjects. The P132H substitution is notable as it emerged in 2 subjects ([redacted] (b) (6)) and this represents the only consensus M^{pro} amino acid polymorphism in SARS-CoV-2 Omicron lineages relative to previous lineages, and thus would raise concerns that PAXLOVID has reduced activity against SARS-CoV-2 Omicron lineages. However, a closer examination of the sequencing data indicates the detection of P132H in these subjects is likely due to laboratory contamination or some other technical artifact. In both subjects the substitution was detected only in Day 3 samples but not in Baseline or Day 5 samples, and in both Day 3 samples several additional Omicron signature amino acid changes were detected in Spike and other viral proteins. Further investigation by the Applicant found 17 other cases of low-level detection (<10% frequency) of P132H, all in single samples from different subjects. Of the 19 samples with P132H detected, 17 (including the Day 3 samples from subjects [redacted] (b) (6)) were analyzed on the same date [redacted] (b) (6)) after the emergence of the Omicron variant (Applicant's response to September 16, 2022, information request (Pfizer 2022o)). Three other PAXLOVID-treated subjects had treatment-emergent P132L (n = 1) or P132S (n = 2). None of these amino acid changes at position P132 (H, L or S) have been shown to affect nirmatrelvir activity in biochemical or cell-based assays, so the relevance of any P132 TES is unclear. In addition, using X-ray crystallography, the Applicant has demonstrated that P132H is located distal (~16 Å) to the NIR binding pocket and does not significantly affect the conformation of the binding pocket or the binding of nirmatrelvir to the enzyme (Greasley et al. 2022). See Section 18.3.4 for additional

independent analyses of this position from the raw NGS data. Note that no P132 TES were observed in EPIC-SR.

- M^{pro} G11C/S/V or T111I were detected as TES at low amino acid frequencies (≤16% in all cases) across 6 PAXLOVID-treated subjects. These positions are outside of the nirmatrelvir binding site and are not known to be associated with nirmatrelvir resistance. In EPIC-SR, no PAXLOVID recipients had a T111 TES, and 1 PAXLOVID versus 3 placebo recipients had a G11A/R/V TES. Thus, G11 and T111 substitutions are considered unlikely to be associated with nirmatrelvir resistance. The Applicant will be requested to phenotypically characterize the impact of G11V (observed in 2 PAXLOVID recipients across EPIC-HR and EPIC-SR) on nirmatrelvir activity as a post-marketing requirement.
- A small number of M^{pro} cleavage site (CS) substitutions appeared to emerge preferentially in PAXLOVID-treated subjects, including CS#2 (nsp5/nsp6) A3571V and CS#8 (nsp12/nsp13) A5328P/S. Of note, CS#8 (nsp12/nsp13) A5328S/V was also observed as a PAXLOVID TES in EPIC-SR. As shown in Table 197, there were no clear patterns of association between these M^{pro} cleavage site TES and M^{pro} TES. In independent FDA analyses of the raw NGS data (Section 18.3.4), the A3571V TES was identified in 3 PAXLOVID-treated subjects and 2 placebo-treated subjects, and thus was not considered enriched in the PAXLOVID arm. In contrast, the A5328P/S TES was not identified (using a 10% frequency threshold) in any subjects. However, two other potential PAXLOVID M^{pro} cleavage site TES were identified. To our knowledge, other than the M^{pro} T304I substitution, which overlaps the nsp5/nsp6 cleavage site as discussed above, no phenotypic data have been reported regarding the impact of amino acid changes in any M^{pro} cleavage site on SARS-CoV-2 susceptibility to nirmatrelvir. Of note, A3571V is one of the most common naturally occurring polymorphisms in M^{pro} cleavage sites (Section 18.4).

Table 197. Subjects With PAXLOVID Treatment-Emergent Amino Acid Substitutions at M^{pro} Cleavage Sites (CS#2 A3571V, CS#8 A5328P/S), and Other Detected Treatment-Emergent M^{pro} Substitutions

USUBJID	Arm	Tx-Emergent Substitution(s) (AA frequency)	Tx-Emergent M^{pro} Substitution(s) (AA frequency)
(b) (6)	Placebo	CS#2 A3571V (>0.99)	V73I (0.10)
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#2 A3571V (>0.99)	None
	PAXLOVID	CS#8 A5328S (0.10)	L30F (0.11)
	PAXLOVID	CS#8 A5328S (0.19)	None
	PAXLOVID	CS#8 A5328P (0.13)	V186G (0.16)
	PAXLOVID	CS#8 A5328S (0.34)	None

Source: FDA analysis of NGS analysis dataset.
Abbreviations: AA, amino acid; CS, cleavage site; M^{pro}, main protease; NGS, next-generation sequencing; Tx, treatment; USUBJID; unique subject identified

Detailed baseline resistance analyses could not be conducted due the conserved nature of the M^{pro} amino acid sequence and the low frequency of subjects with amino acid polymorphisms detected at M^{pro} positions potentially associated with nirmatrelvir resistance. Only 10 (1.4%) PAXLOVID-treated subjects had an amino acid polymorphism detected at a potential nirmatrelvir resistance-associated position in M^{pro} (Figure 87). Viral RNA levels over time in

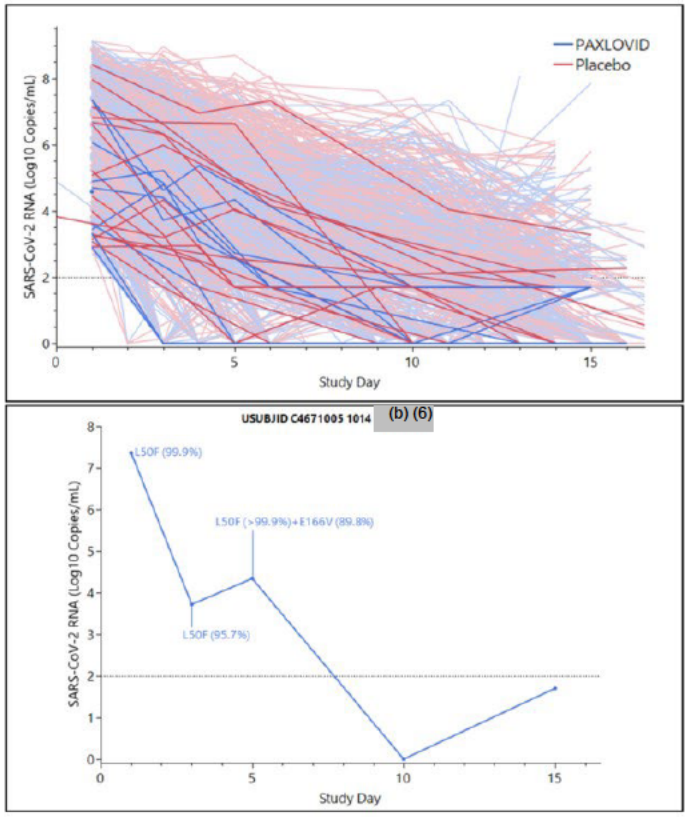
these subjects were generally consistent with other subjects, and none of the subjects reached the primary endpoint of hospitalization or death.

Although the baseline resistance analyses were limited by the small number of subjects infected with viruses with M^{pro} polymorphisms, there was one notable example of a subject (SUBJID (b) (6)) with a predominant (~99.9% frequency) M^{pro} L50F polymorphism. The subject had a treatment-emergent M^{pro} E166V (~90% frequency) substitution detected in the Day 5 visit sample, which was associated with a ~0.6 log_{10} copies/mL increase in viral RNA level during treatment between Day 3 and Day 5/End-of-treatment (Figure 87). As noted above, E166V was a clear treatment-emergent nirmatrelvir RAS. In a biochemical assay, L50F alone did not reduce nirmatrelvir activity, but the combination of L50F + E166V was associated with high level nirmatrelvir resistance (4,500-fold increase in K_i value). Furthermore, both Iketani et al and Zhou et al. reported that recombinant viruses with L50F + E166V had enhanced replication capacity compared to those with only the E166V substitution, indicating L50F may serve as a compensatory fitness substitution for viruses with E166V (Zhou et al. 2022b; Iketani et al. 2023). Although observed in only one participant in EPIC-HR, this observation provides a clear example of how a specific baseline M^{pro} polymorphism could contribute to nirmatrelvir resistance.

Figure 87. EPIC-HR: Frequency of Detection of M^{pro} Polymorphisms and Their Association With Viral RNA Responses

Baseline M^{pro} Polymorphism*	PAXLOVID	Placebo
L50F	1	2
P108L	1	1
P108S	1	3
E166K	0	1
T169P	1	0
Q189K	2	6
T190I	1	0
A191V	0	1
Q192L	1	0
A193V	2	1
T190P, A191V, Q192R	0	1
Any	1.4% (10/719)	2.3% (16/694)

*Based on 10% frequency cutoff, considering any M^{pro} change at (1) contact binding site residue, or (2) position associated with resistance in cell culture



Source: FDA analysis of ADMC and NGS analysis datasets.
Note: In the top figure panel, lines in the foreground represent individual subjects with one of the noted M^{pro} baseline polymorphisms detected, and lines in the background represent all other subjects.
Note: Dashed lines indicate the assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; M^{pro}, main protease; NGS, next-generation sequencing; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SUBJID, unique subject identifier

18.3.3. EPIC-SR: SARS-CoV-2 Variants and Resistance Analyses

The EPIC-SR analyses summarized below were conducted using the NGS analysis dataset submitted on December 21, 2022, during the review cycle.

Of the 1288 subjects enrolled in EPIC-SR (after site censoring), SARS-CoV-2 variant assignments were available from 1006 (78%) subjects. Variant results separated by enrollment period are summarized in Table 198. SARS-CoV-2 Delta variants were predominant in the 2021 enrollment period, while 100% of variants were identified with an Omicron variant (96%) or Omicron-containing recombinant (4%) in the 2022 enrollment period. Among those with Omicron variant infections (n = 188, excluding recombinants), the most common PANGO lineages identified were BA.2 (38%), BA.2.9 (22%), and BA.2.12.1 (10%).

Table 198. SARS-CoV-2 Variants Detected in EPIC-SR

		2021 Enrollment Period			2022 Enrollment Period		
WHO Variant	Nextstrain Clade	Paxlovid (n=418)	Placebo (n=393)	All Subjects (n=811)	Paxlovid (n=98)	Placebo (n=97)	All Subjects (n=195)
Delta	21A	11 (3%)	21 (5%)	32 (4%)	0	0	0
	21I	45 (11%)	43 (11%)	88 (11%)	0	0	0
	21J	356 (85%)	320 (81%)	676 (83%)	0	0	0
	All Delta	412 (99%)	384 (98%)	796 (98%)	0	0	0
Omicron	21K	0	0	0	3 (3%)	4 (4%)	7 (4%)
	21L	0	0	0	69 (70%)	63 (65%)	132 (68%)
	22A	0	0	0	8 (8%)	7 (7%)	15 (8%)
	22B	0	0	0	5 (5%)	8 (8%)	13 (7%)
	22C	0	0	0	10 (10%)	11 (11%)	21 (11%)
	All Omicron	0	0	0	95 (97%)	93 (96%)	188 (96%)
Gamma	20J	5 (1%)	5 (1%)	10 (1%)	0	0	0
Lambda	21G	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
Mu	21H	0	3 (<1%)	3 (<1%)	0	0	0
Recombinant		0	0	0	3 (3%)	4 (4%)	7 (4%)*

Source: FDA analysis of ADSL and NGS analysis datasets (updated/final NGS dataset submitted December 21, 2022).
* Omicron recombinants XZ (n=6) or XE (n=1).
Abbreviations: n, number of subjects in sample; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

Resistance analyses were conducted for EPIC-SR following a similar analysis approach as conducted for EPIC-HR.

A total of 784 subjects (n = 382 PAXLOVID, n = 402 Placebo) had baseline and post-baseline viral sequencing data available. This includes 140 subjects with an Omicron variant infection (n = 64 PAXLOVID, n = 76 Placebo). As for EPIC-HR, a 10% frequency cutoff was used to identify amino acid changes relative to reference. Also, a similar algorithm was used to identify treatment-emergent amino acid changes associated with PAXLOVID treatment:

- Unbiased analysis: Amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (≥0.8% of subjects), and at a ≥2-fold greater frequency than in Placebo-treated subjects, considering all available timepoints from subjects with baseline and at least one post-baseline result.

- Any treatment-emergent amino acid changes at any of the following NIR M^{pro} contact residues (within 5 Å) (“CR”): H41, M49, Y54, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166, L167, P168, H172, V186, D187, R188, Q189, T190, A191, Q192
- Any treatment-emergent amino acid changes at any M^{pro} residues associated with NIR phenotypic resistance in cell culture (Section 20.3, partially overlaps with contact residues) (“Ph”): T21, L50, P108, T135, F140, S144, C160, E166, L167, T169, H172, A173, V186, R188, A191, A193, P252, S301, T304

Results from these analyses are summarized in Table 199.

Table 199. PAXLOVID Treatment-Emergent Amino Acid Substitutions Observed in EPIC-SR

AA Position and Substitution(s)	Reporting Criteria[1]	# PAX-Tx Subjects (n=382 w/ data)	# PBO-Tx Subjects (n=402 w/ data)	AA Frequency in PAX-Tx Subjects[2]	Hosp. or Death Endpt (PAX-Tx Subjects)	NIR Fold-Change (AA)[3]
M^{pro} Amino Acid Substitutions						
L50F	Ph	1	0	0.11	N	1.5(c) 0.2(b)
T98I/R	TE	3 (2I,1R)	0	0.12-0.15	N	nd
P108S	Ph	1	0	0.10	N	2.9(b)
H172del	CR/Ph	1	0	0.13	N	nd (del), 250(b) (Y)
Q189K	CR	7	11	0.10-0.54	N	0.2(c) <1.6(b)
S301L	Ph	1	0	0.11	N	nd (L), 0.2(b) (P)
Any	TE, CR or Ph	12 (3%)	11 (3%)			
Any	CR or Ph	10 (3%)	11 (3%)			
M^{pro} Cleavage Site Amino Acid Substitutions						
CS#8 A5328S/V	TE	4 (2S,2V)	0	0.10-0.37	N	nd

Source: FDA analysis of NGS analysis dataset.

[1] Substitutions detected in PAXLOVID-treated subjects meeting one or more of the following criteria:

- TE: treatment-emergent in ≥3 PAXLOVID-treated subjects (i.e., ≥0.8% of subjects) at the same amino acid position in M^{pro} or M^{pro} cleavage site, AND ≥2-fold more frequently in PAXLOVID-treated subjects relative to placebo-treated subjects.
- CR: emerged in ≥1 PAXLOVID-treated subject at a nirmatrelvir contact residue in M^{pro} (w/in 5 Å); 'Any' calculations included substitutions only detected in Placebo-treated subjects.
- Ph: emerged in ≥1 PAXLOVID-treated subject at a residue in M^{pro} associated with NIR phenotypic resistance in cell culture (i.e., emerged in selection studies and/or shown to confer reduced NIR activity in cell culture); 'Any' calculations included substitutions only detected in Placebo-treated subjects).

[2] Amino acid frequency ≥10% considered for detection.

[3] Based on EC_{50} value in cell culture assay:

- (c) or IC_{50} value in biochemical assay
- (b). nd, no data

Abbreviations: AA, amino acid; C, cysteine; CS, cleavage site; del, deletion; EC_{50}, half-maximal effective concentration; Endpt, endpoint; F, phenylalanine; H, histidine; I, isoleucine; Hosp, hospitalization; IC_{50}, half-maximal inh bitory concentration; L, leucine; M^{pro}, main protease; N, no; n, number of subjects in sample; nd, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; P, proline; PAX, paxlovid; R, arginine; S, serine; Tx, treated; w/, with; Y, tyrosine

Key observations from these analyses include the following:

- Overall, as in EPIC-HR, the detection of PAXLOVID treatment-emergent viral populations potentially resistant to nirmatrelvir was uncommon. Considering nirmatrelvir contact residues ("CR" positions) and positions shown to be associated with phenotypic resistance in cell culture ("Ph" positions), 10 (3%) of PAXLOVID recipients and 11 (3%) of placebo recipients had a TES detected at one of these positions, indicating no clear signal of potential resistance emergence associated with PAXLOVID treatment.
- Other noted TES in M^{pro} generally occurred in small numbers of PAXLOVID recipients and at low amino acid frequencies, with the exception of Q189K which was not associated with PAXLOVID treatment (also observed and noted as potentially common sequence artifact in EPIC-HR).
- The M^{pro} H172del TES was observed in 1 PAXLOVID recipient. Although observed only in a single subject (and not in EPIC-HR), this change is notable as another substitution at this position (H172Y) conferred a 250-fold reduction in nirmatrelvir activity in a biochemical assay, and the deletion in theory would be more difficult to generate spontaneously during viral replication. The change was observed in Day 14 sequences at a 13% frequency, but not in Day 1, 3, 5, or 10 sequences from the subject. Independent FDA analyses of the raw fastq data from this subject confirmed the detection of H172del (7.2% frequency by FDA analysis) in the Day 14 sequences but not the other sequences. The change was created by the deletion of 3 nucleotides (ATG) spanning the codons for H172 and A173 (H172-A173del, insP), and sequences from Day 14 were clearly of lower quality relative to the other sequences as reflected by larger numbers of changes throughout the M^{pro} coding sequence, including several frameshifts and stop codons. Thus, it is unclear if H172del truly emerged or if its detection reflects a sequencing artifact.
- M^{pro} S301L emerged in 1 PAXLOVID-treated subject at a 0.11 frequency. An S301P substitution emerged in a cell culture drug resistance selection study but this change did not reduce NIR activity in a biochemical assay. This position overlaps with the P6 position of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}.
- In contrast with the results from EPIC-HR, no PAXLOVID TES were observed at M^{pro} positions T111, P132, or A260. Interestingly, A260P/V TES were observed in 4 placebo recipients. Also, 3 placebo recipients and 1 PAXLOVID recipient had a TES at position G11 (A/R/V).
- The M^{pro} CS#8 (nsp12/nsp13) substitution A5328S/V emerged in 4 PAXLOVID recipients and 0 placebo recipients. No other M^{pro} or M^{pro} cleavage site TES were detected in these subjects. Of note, A5328P/S was identified as a potential PAXLOVID TES in EPIC-HR (depending on specific analysis). Additional phenotypic characterizations of this cleavage site position are warranted to assess a potential role in nirmatrelvir resistance.
- Of the PAXLOVID TES indicated above, only the M^{pro} cleavage site TES A5328V was observed in 1 subject who enrolled in the 2022/Omicron period; all other TES noted for PAXLOVID recipients were observed among subjects who enrolled in the 2021/Pre-Omicron period.
- No subjects with any of the noted M^{pro} or M^{pro} cleavage site TES experienced the endpoint of hospitalization or death, consistent with the low number of such events overall in the trial.

Overall, these results from EPIC-SR are consistent with those from EPIC-HR in that PAXLOVID TES potentially associated with nirmatrelvir resistance were infrequently observed.

18.3.4. EPIC-HR: Independent FDA Analyses of Raw NGS Data

Methods

The Applicant's NGS data from EPIC-HR were independently analyzed using the High-Performance Integrated Virtual Environment (HIVE) (Simonyan and Mazumder 2014). HIVE contains specific tools that allow the reviewer to batch rename files to meet nomenclature rules for the analysis pipeline, to assess the quality of sequence files, to align sequence reads to a reference sequence and identify variants, and to convert variant call files into amino acid frequency tables. The workflow in HIVE was as follows: 1) sequence reads were imported and mapped to the reference sequence using the Hexagon aligner tool, 2) variants were called at the amino acid level using the Heptagon profiling tool, and 3) amino acid frequency tables were generated using the Viral Mutation Comparator tool. Each step of the analysis process is described in more detail below.

Preparing Fastq Files and Reference Sequences

Data files were submitted to the FDA on a portable hard drive, which included fastq file pairs for every sample that was sequenced. The fastq files were uploaded into HIVE and assessed for quality control by analyzing the following parameters: the overall proportion of each nucleotide (G/C/A/T), the average quality of each nucleotide, average sequence length, average sequence quality, and the count and average quality of each nucleotide by read position. For analysis of M^{pro} substitutions, the SARS-CoV-2 Wuhan-Hu-1 M^{pro} sequence was uploaded as the reference sequence for mapping (NCBI 045512.2). For analysis of M^{pro} cleavage sites, the SARS-CoV-2 Wuhan-Hu-1 pp1ab sequence was uploaded as the reference sequence for mapping.

Mapping Reads to the Reference Sequences

Sequence reads were mapped to the appropriate reference sequence using the Hexagon aligner tool in HIVE. Default analysis parameters were applied, including local alignment, match benefit: 5, mismatch penalty: -4, mismatch continuation penalty: -6, gap continuation cost: -4, gap opening cost: -12, minimum match of 40 nucleotides, and 15% mismatches allowed. The output files were assessed to determine the proportions of mapped reads, the lengths of aligned segments, and sequencing coverage for each sample.

Generating Amino Acid Frequency Tables

Next, variants were called using the HIVE Heptagon Sequence Profiler tool (Simonyan et al. 2017). Default analysis parameters were applied. Variant call tables were converted into amino acid frequency tables using the HIVE Viral Mutation Comparator tool, with a substitution frequency threshold of 1%. Synonymous mutations were excluded. The amino acid frequency table contains information for each position and each sample for which variation from the reference was detected. The frequency table contains the following columns: unique subject identifier (USUBJID), visit (VISIT), the amino acid position within the protein of interest

(AAPOS), the amino acid found in the reference sequence (AAREF), the amino acid substitution (AASUB), the frequency at which the variant was detected (AAFREQ), the coverage at the nucleotide level for the variant (VCOV), and the total coverage at the nucleotide position (TCOV). Two additional columns were manually added to the table based on information from the Applicant's datasets: actual treatment (TRT01A) and a flag for hospitalization/death through Day 28 (HPDTHFL).

Analyzing Amino Acid Frequency Tables

Amino acid frequency tables from HIVE were analyzed using custom Python scripts and various analysis criteria, which are described in the results sections below. Most analyses were focused on baseline polymorphisms and TES that were detected at a frequency ≥10%, due to the high frequency of probable sequencing artifacts (as indicated by M^{pro} premature stop codons) below this threshold. The 10% threshold excluded ~96% of M^{pro} premature stop codons with a frequency >1%.

Results

Characterization of Dataset

After excluding censored subjects, the Applicant provided sequencing data for 3,573 samples from 1,526 subjects. Overall, M^{pro} amino acid substitution frequency results were obtained for 3,563 (99.7%) samples, including 1,714 samples from PAXLOVID-treated subjects, 1,843 samples from placebo-treated subjects, and 6 samples from untreated subjects (Table 200). Results from at least one sample were obtained for 1,525 (99.9%) subjects, including 763 PAXLOVID-treated subjects, 757 placebo-treated subjects, and 5 untreated subjects (Table 201). Results from baseline and at least one post-baseline sample were obtained for 537/763 (70.4%) of PAXLOVID-treated subjects and 550/757 (72.7%) of placebo-treated subjects. Results from untreated subjects were excluded from further analyses.

Table 200. Samples With M^{pro} Amino Acid Substitution Frequency Results

Treatment	# Baseline/ Day 1 Samples	# Day 3 Samples	# Day 5 Samples	# Day 10 Samples	# Day 14 Samples	Total
PAXLOVID	718	497	358	107	34	1,714
Placebo	693	539	429	133	49	1,843
Untreated	5	0	1	0	0	6
Total	1,416	1,036	788	240	83	3,563

Source: FDA analysis of raw NGS fastq data.
Abbreviations: M^{pro}, main protease; NGS, next-generation sequencing

Table 201. Subjects With Baseline and/or Post-Baseline M^{pro} Amino Acid Substitution Frequency Results

Treatment	# Subjects	# Subjects With Baseline Sample	# Subjects With ≥1 Post-Baseline Sample	# Subjects With Baseline and ≥1 Post-Baseline Sample
PAXLOVID	763	717	583	537
Placebo	757	693	614	550
Untreated	5	5	1	1
Total	1,525	1,415	1,198	1,088

Source: FDA analysis of raw NGS fastq data.
Abbreviations: M^{pro}, main protease; NGS, next-generation sequencing

Identification of Baseline M^{pro} Polymorphisms at Positions of Interest

Baseline M^{pro} amino acid polymorphisms with frequencies ≥10% were analyzed at 34 residues that are considered positions of interest (Table 202), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. Baseline polymorphisms were identified at 12/34 positions of interest. The M^{pro} Y54S and N142D polymorphisms are considered likely to be sequencing artifacts, as they were identified in many subjects in both arms, usually had low frequencies, and occurred at residues that are highly conserved (>99.99%) in the GISAID sequence database. Excluding Y54S and N142D, baseline polymorphisms at positions of interest were identified in 9/717 (1.3%) of PAXLOVID-treated subjects and 14/693 (2.0%) of placebo-treated subjects. Baseline polymorphisms at these positions were not significantly associated with hospitalization or death in either treatment arm.

Table 202. Baseline M^{pro} Amino Acid Polymorphisms at 34 Positions of Interest

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=717 w/ data)	# PBO-Tx Subjects (n=693 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
T21	N/A	0	0	N/A	N/A	N/A
H41	N/A	0	0	N/A	N/A	N/A
M49	N/A	0	0	N/A	N/A	N/A
L50	L50F	1	2	0.68, 0.21-0.84	No, No	1.4-4.2
Y54	Y54S	711	688	0.10-0.74, 0.10-0.73	Yes (10/711), Yes (60/688)	ND
P108	P108L/S	2	4	0.10-0.13, 0.37-0.82	No, No	ND
T135	N/A	0	0	N/A	N/A	N/A
F140	N/A	0	0	N/A	N/A	N/A
L141	N/A	0	0	N/A	N/A	N/A
N142	N142D	57	65	0.10-0.72, 0.10-0.76	No, Yes (4/65)	ND
G143	N/A	0	0	N/A	N/A	N/A
S144	N/A	0	0	N/A	N/A	N/A
C145	N/A	0	0	N/A	N/A	N/A
C160	N/A	0	0	N/A	N/A	N/A
H163	N/A	0	0	N/A	N/A	N/A
H164	N/A	0	0	N/A	N/A	N/A
M165	N/A	0	0	N/A	N/A	N/A
E166	E166K	0	1	N/A, 0.1	N/A, No	ND
L167	N/A	0	0	N/A	N/A	ND
P168	N/A	0	0	N/A	N/A	N/A
T169	T169P	1	0	1.0, N/A	No, N/A	ND
H172	N/A	0	0	N/A	N/A	N/A
A173	N/A	0	0	N/A	N/A	N/A
V186	N/A	0	0	N/A	N/A	N/A
D187	D187S	1	1	0.32, 0.16	No, No	ND
R188	R188I	1	1	0.32, 0.16	No, No	ND
Q189	N/A	0	0	N/A	N/A	N/A
T190	T190I	1	0	0.30, N/A	No, N/A	ND
A191	A191V	0	1	N/A, 0.39	N/A, No	ND
Q192	Q192K	1	0	0.10, N/A	No, N/A	ND
A193	A193E/V	2	5	1.0, 0.1-1.0	No, Yes (1/5)	ND

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=717 w/ data)	# PBO-Tx Subjects (n=693 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
P252	N/A	0	0	N/A	N/A	N/A
S301	N/A	0	0	N/A	N/A	N/A
T304	N/A	0	0	N/A	N/A	N/A

Source: FDA analysis of raw NGS fastq data.
Note: Grey shading indicates positions at which baseline polymorphisms were not observed in any subjects.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next-generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; PBO, placebo; Tx, treated

Identification of M^{pro} Treatment-Emergent Substitutions (TES) Associated With PAXLOVID

Next, M^{pro} TES were identified, which were defined as substitutions that had a frequency <10% at baseline and a frequency ≥10% in at least one post-baseline sample from the same subject. Subsequently, TES associated with PAXLOVID treatment were identified, which were defined as TES that emerged in at least three more PAXLOVID-treated subjects than placebo-treated subjects. This analysis was performed using two methods. In method #1, different substitutions at the same position (e.g., G23D and G23S) were considered independently. In method #2, all substitutions at the same position were grouped together. The same results were obtained regardless of whether premature stop codons were included or excluded from the analysis. With method #1, two M^{pro} TES were identified: G23S and E166V (Table 203). With method #2, 4 M^{pro} TES were identified: G23D/S/V, C85R/Y, E166V, and T199I/P/S (Table 204). The E166V TES is considered likely to be a resistance-associated substitution (RAS), as it was observed only in the PAXLOVID arm, occurred at high frequencies (26 to 94%), and has been associated with NIR resistance in cell culture (Zhou et al. 2022b; Iketani et al. 2023). It is unclear whether the other TES represent RAS, as they were usually observed in both arms (except C85R/Y), often had low frequencies, and did not occur at positions that contact NIR, are located in close proximity of NIR, or have been associated with NIR resistance in cell culture. These M^{pro} TES were not significantly associated with hospitalization or death. The E166V TES was also identified by FDA analysis of the Applicant's amino acid frequency table.

Table 203. M^{pro} TES Enriched in PAXLOVID-Treated Subjects (Method #1)

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
G23S	18	10	0.10-0.12, 0.10-0.13	No, Yes (1/10)	No	ND
E166V	3	0	0.26-0.94, N/A	No, N/A	Yes	25-288

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; TES, treatment-emergent substitution; Tx, treated

Table 204. M^{pro} TES Enriched in PAXLOVID-Treated Subjects (Method #2)

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
G23D/S/V	23	17	0.10-0.12, 0.10-0.16	No, Yes (2/17)	No	ND
C85R/Y	3	0	0.11-0.14, N/A	No, N/A	No	ND

AA Substitution	# PAX-Tx Subjects (n=537 w/ data)	# Placebo-Tx Subjects (n=550 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt? (PAX-Tx, Placebo-Tx)	Position of Interest?	NIR EC_{50} Fold-Change
E166V	3	0	0.26-0.94, N/A	No, N/A	Yes	25-288
T199I/P/S	5	2	0.10-0.39, 0.12-0.16	Yes (1/5), No	No	ND

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; M^{pro}, main protease; n, number of subjects; N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; TES, treatment-emergent substitution; Tx, treated

Identification of M^{pro} TES at Positions of Interest

Next, M^{pro} TES (defined as described above) were analyzed at 34 residues that are considered positions of interest (Table 205), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. This analysis included all TES at positions of interest, regardless of whether they were enriched in the PAXLOVID arm. M^{pro} TES were identified at 17/34 positions of interest. The M^{pro} Y54S and N142D TES are considered likely to be sequencing artifacts, as they were identified in many subjects at baseline in both arms (Table 202), usually had low frequencies, and occurred at residues that are highly conserved (>99.99%) in the GISAID sequence database. Excluding Y54S and N142D, TES at positions of interest were identified in 12/537 (2.2%) of PAXLOVID-treated subjects and 5/550 (0.9%) of placebo-treated subjects. As described above, the E166V TES is considered likely to be a RAS. It is unclear whether any of the other TES represent RAS, as they were not clearly associated with PAXLOVID treatment and often occurred at low frequencies. The T21I and T304I substitutions have been associated with NIR resistance in cell culture. The TES in the PAXLOVID arm were not significantly associated with hospitalization or death. The C145F, C160R, E166V, A173T, and T304I TES were also identified by FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196).

Table 205. M^{pro} TES at 34 Positions of Interest

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=537 w/data)	# PBO-Tx Subjects (n=550 w/data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
T21	T21I	1	0	0.11, N/A	No, N/A	1.1-4.6
H41	N/A	0	0	N/A	N/A	N/A
M49	N/A	0	0	N/A	N/A	N/A
L50	N/A	0	0	N/A	N/A	N/A
Y54	Y54S	0	3	N/A, 0.12-0.63	N/A, Yes (2/3)	ND
P108	N/A	0	0	N/A	N/A	N/A
T135	N/A	0	0	N/A	N/A	N/A
F140	N/A	0	0	N/A	N/A	N/A
L141	N/A	0	0	N/A	N/A	N/A
N142	N142D	37	60	0.10-0.20, 0.10-0.36	No, Yes (5/60)	ND
G143	N/A	0	0	N/A	N/A	N/A
S144	N/A	0	0	N/A	N/A	N/A
C145	C145F/H	1	0	0.10-0.17, N/A	No, N/A	ND
C160	C160R/[a]	2	0	0.15-0.32, N/A	No, N/A	ND
H163	N/A	0	0	N/A	N/A	N/A
H164	N/A	0	0	N/A	N/A	N/A

M^{pro} Residue	AA Substitution	# PAX-Tx Subjects (n=537 w/data)	# PBO-Tx Subjects (n=550 w/data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
M165	N/A	0	0	N/A	N/A	N/A
E166	E166V	3	0	0.26-0.94, N/A	No, N/A	25-288
L167	N/A	0	0	N/A	N/A	N/A
P168	N/A	0	0	N/A	N/A	N/A
T169	T169S	0	1	N/A, 0.13	N/A, No	ND
H172	N/A	0	0	N/A	N/A	N/A
A173	A173N/T	2	1	0.13-0.20, 0.11	No, No	ND
V186	V186L	1[b]	1	0.11, 0.16	No, No	ND
D187	D187Y	1[b]	0	0.11, N/A	No, N/A	ND
R188	R188K	1[b]	0	0.11, N/A	No, N/A	ND
Q189	N/A	0	0	N/A	N/A	N/A
T190	T190P	1[b]	0	0.11, N/A	No, N/A	ND
A191	A191P	1[b]	0	0.11, N/A	No, N/A	ND
Q192	Q192[a]	1	0	0.33, N/A	No, N/A	ND
A193	A193V	0	1	N/A, 0.20	N/A, No	ND
P252	P252H	0	1	N/A, 0.10	N/A, No	ND
S301	N/A	0	0	N/A	N/A	N/A
T304	T304I	1	0	0.24, N/A	No, N/A	2.1-5.5

Source: FDA analysis of raw NGS fastq data.
Note: Grey shading indicates positions at which TES were not observed in any subjects.
[a] Stop codon
[b] same subject
Abbreviations: AA, amino acid; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; n, number of subjects N/A, not applicable; ND, no data; NGS, next generation sequencing; NIR, nirmatrelvir; Pax, Paxlovid; PBO, placebo; TES, treatment-emergent substitution; Tx, treated

Identification of M^{pro} Cleavage Site TES Associated With PAXLOVID

Next, M^{pro} cleavage site TES associated with PAXLOVID treatment were identified, defined as in section C. This analysis was performed using two methods. In method #1, different substitutions at the same position were considered independently, and in method #2, all substitutions at the same position were grouped together. With method #1, one M^{pro} cleavage site TES was identified: K6796T (pp1ab numbering), which is located in the P3 position of the nsp15/nsp16 cleavage site (Table 206). With method #2, one other M^{pro} cleavage site TES was identified: M3862I/K, which is located in the P3′ position of the nsp6/nsp7 cleavage site. It is unclear whether these TES represent RAS, as they were observed in both arms, often had low frequencies, and have not been associated with NIR resistance in cell culture. These TES were not associated with hospitalization or death.

Table 206. M^{pro} Cleavage Site (CS) TES Enriched in PAXLOVID-Treated Subjects

Method	AA Substitution	CS, Position	# PAX-Tx Subjects (n=528 w/ data)	#PBO-Tx Subjects (n=544 w/ data)	AA Freq (PAX-Tx, Placebo-Tx)	Hosp. or Death Endpt (PAX-Tx, Placebo-Tx)	NIR EC_{50} Fold-Change
#1	K6796T	nsp15/nsp16, P3	6	2	0.10-0.29, 0.10-0.18	No, No	ND
#2	M3862I/K	nsp6/nsp7, P3′	5	2	0.10-0.12, 0.10-0.11	No, No	ND

Source: FDA analysis of raw NGS fastq data.
Abbreviations: AA, amino acid; CS, cleavage site; EC_{50}, half maximal effective concentration; Endpt, endpoint; Freq, frequency; Hosp, hospitalization; n, number of subjects; N/A, not applicable; ND, no data; NG, next-generation sequencing; nsp, nonstructured protein; NIR, nirmatrelvir; PAX, Paxlovid; PBO, placebo; TES, treatment-emergent substitution; Tx, treated

Additional Analysis of M^{pro} E166V Substitutions

Additional analysis was performed to further characterize the M^{pro} E166V substitution, which was considered likely to be a RAS. As described in section C, the E166V TES was identified in 3 PAXLOVID-treated subjects and 0 placebo-treated subjects. None of these subjects experienced hospitalization or death. For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 5. The E166V substitution was detected with a frequency of 90% on Day 5 but was not detected on Days 1 or 3 (frequency <1%). The M^{pro} L50F polymorphism was also detected in this subject on Day 1 (68%), Day 3 (82%), and Day 5 (85%). For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 10. The E166V substitution was detected with a frequency of 26% on Day 10 but was not detected on Days 1 or 3. For subject (b) (6), sequencing results were available from samples collected on Days 1, 3, and 5. The E166V substitution was detected with a frequency of 94% on Day 5 but was not detected on Days 1 or 3.

Additional analyses were performed to determine whether the M^{pro} E166V substitution was detected at a frequency ≥1% in any additional subjects. The E166V substitution was only identified in 1 additional subject, who was treated with PAXLOVID. This subject did not experience hospitalization or death. For this subject, sequencing results were available from samples collected on Days 1, 3, 5, 10, and 14. The E166V substitution was only detected on Day 5, with a frequency of 2%. The E166V substitution was not detected in samples from any other subjects, including post-baseline samples from subjects who were missing baseline samples. Thus, overall, the E166V substitution was detected in 4/537 (0.7%) of PAXLOVID-treated subjects with baseline and post-baseline samples and 4/583 (0.7%) of PAXLOVID-treated subjects with at least one post-baseline sample.

Additional Analysis of M^{pro} P132H/L/S Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} P132H/L/S TES was identified in 5 PAXLOVID-treated subjects and 0 placebo-treated subjects. However, as described in Section 18.3.2, the two instances of P132H appeared to be due to contamination with Omicron sequences, based on detection of other Omicron-specific changes. After excluding P132H, the M^{pro} P132L/S TES was identified in 3 PAXLOVID-treated subjects (at frequencies of 19 to 35%) and 0 placebo-treated subjects. In FDA analysis of the Applicant's raw NGS data, the M^{pro} P132T TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject and 0 placebo-treated subjects. Thus, the M^{pro} P132T TES was not considered enriched in the PAXLOVID arm and was not included in Table 203 and Table 204.

Further analysis revealed that the P132L/S/T TES were detected by the FDA in the same 3 PAXLOVID-treated subjects identified by the Applicant, but at lower frequencies (5-12%) that were below the 10% cutoff in 2/3 subjects (Table 207). When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the P132L/S/T TES were detected in 4 PAXLOVID-treated subjects and 0 placebo-treated subjects. With an even lower 1% frequency cutoff, the P132A/L/S/T TES were detected in 9 PAXLOVID-treated subjects and 8 placebo-treated subjects. The M^{pro} P132H/L/S substitutions did not affect nirmatrelvir activity in biochemical and/or cell culture assays.

Table 207. Analysis of 3 PAXLOVID-Treated Subjects With M^{pro} P132L/S TES

SUBJID	Applicant's Analysis	FDA Analysis
(b) (6)	P132S detected on Day 5 (35%) but not Days 1 or 10 (<1%)	P132S detected on Day 5 (5%) but not Days 1 or 10 (<1%)
	P132S detected on Day 10 (26%) but not Day 1 (<1%)	P132T detected on Day 10 (12%) but not Day 1 (<1%)
	P132L detected on Day 5 (19%) but not Days 1 or 3 (<1%)	P132L detected on Day 5 (5%) but not Days 1 or 3 (<1%)

Source: FDA analysis of raw NGS fastq data.
Abbreviations: NGS, next-generation sequencing; SUBJID, subject identifier; TES, treatment-emergent substitution

Additional Analysis of M^{pro} V186G Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} V186G TES was identified in 22 PAXLOVID-treated subjects (average frequency: 15%, range: 10-24%) and 15 placebo-treated subjects (average frequency: 15%, range: 10-22%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} V186L TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject (frequency: 11%) and 1 placebo-treated subject (frequency: 16%). However, the V186G TES was not observed in any subjects. Further analysis revealed that the V186G TES was detected by the FDA in 20/22 PAXLOVID-treated subjects, but at lower frequencies (average frequency: 4%, range: 1-8%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the V186G TES was detected in 7 PAXLOVID-treated subjects and 6 placebo-treated subjects. With an even lower 1% frequency cutoff, the V186G TES was detected in 29 PAXLOVID-treated subjects and 20 placebo-treated subjects. The M^{pro} V186G substitution did not affect nirmatrelvir activity in a biochemical assay.

Additional Analysis of M^{pro} Q189K Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} Q189K TES was identified in 5 PAXLOVID-treated subjects (at frequencies of 14 to 32%) and 5 placebo-treated subjects (at frequencies of 11 to 31%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} Q189K TES was not identified (with a 10% frequency cutoff) in any subjects. Further analysis revealed that the Q189K TES was detected by the FDA in all 10 subjects, but at lower frequencies (2-6%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the Q189K TES was detected in 2 PAXLOVID-treated subjects and 1 placebo-treated subjects. With an even lower 1% frequency cutoff, the Q189K TES was detected in 47 PAXLOVID-treated subjects and 33 placebo-treated subjects. The M^{pro} Q189K substitution did not affect nirmatrelvir activity in cell culture.

Additional Analysis of M^{pro} A260S/T/V Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the M^{pro} A260S/T/V TES was identified in 7 PAXLOVID-treated subjects (at frequencies of 11 to 21%) and 1 placebo-treated subject (frequency: 11%). In FDA analysis of the Applicant's raw NGS data, the M^{pro} A260T TES was identified (with a 10% frequency cutoff) in 1 PAXLOVID-treated subject (frequency: 11%) and 0 placebo-treated subjects. Further analysis revealed that the A260S/T/V TES was detected by the FDA in all 8 subjects, but at lower frequencies (1 to 11%) that were below the 10% cutoff in 7/8 subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, A260 TES were detected in 5 PAXLOVID-treated subjects and 2 placebo-treated subjects. With an even lower 1% frequency cutoff, A260 TES were detected in 17 PAXLOVID-treated subjects and 12 placebo-treated subjects. The M^{pro} A260S/T/V substitutions did not affect nirmatrelvir activity in a biochemical assay.

Additional Analysis of pp1ab A3571V Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the pp1ab A3571V TES was identified in 3 PAXLOVID-treated subjects (at frequencies >99%) and 1 placebo-treated subject (at a frequency >99%). In FDA analysis of the Applicant's raw NGS data, the A3571V TES was identified (with a 10% frequency cutoff) in 3 PAXLOVID-treated subjects (at frequencies of 89-96%, same subjects identified by the Applicant) and 2 placebo-treated subjects (at frequencies of 27 to 98%, same subject identified by the Applicant and one additional subject). Thus, the A3571V TES was not considered enriched in the PAXLOVID arm and was not included in Table 206. Also note that A3571V is one of the most common naturally occurring M^{pro} cleavage site polymorphisms (Section 18.4).

Additional Analysis of pp1ab A5328P/S Substitutions

In FDA analysis of the Applicant's amino acid frequency table (Section 18.3.2 and Table 196), the pp1ab A5328P/S TES was identified in 4 PAXLOVID-treated subjects (at frequencies of 10 to 34%) and 0 placebo-treated subjects. In FDA analysis of the Applicant's raw NGS data, the A5328P/S TES was not identified (with a 10% frequency cutoff) in any subjects. Further analysis revealed that the A5328P/S TES was detected by the FDA in all 4 subjects, but at lower frequencies (1-7%) that were below the 10% cutoff in all subjects. When FDA analysis of the Applicant's raw NGS data was repeated with a 5% frequency cutoff, the A5328S TES was detected in 1 PAXLOVID-treated subject and 0 placebo-treated subjects. With an even lower 1% frequency cutoff, A5328 TES were detected in 5 PAXLOVID-treated subjects and 2 placebo-treated subjects.

Analysis of Ten Additional Samples in CLC Genomics Workbench

M^{pro} amino acid substitution frequency results were not obtained in HIVE for 10/3,573 (0.3%) samples, including 4 samples from PAXLOVID-treated subjects and 6 samples from placebo-treated subjects. Upon further review, the sequencing results from these ten samples appeared to be of low quality. Specifically, a large portion of the reads appeared to result from non-specific PCR products (e.g., primer dimers). These ten samples were analyzed using a separate bioinformatics pipeline in CLC Genomics Workbench (Qiagen 2023). M^{pro} and M^{pro} cleavage

site substitutions (≥10% frequency) were not detected in any of the 4 samples from PAXLOVID-treated subjects, in agreement with the Applicant's results for these samples.

Conclusions From Independent FDA Analyses of Raw NGS Data

- The M^{pro} E166V TES was confirmed in 3 PAXLOVID-treated subjects. Using a lower frequency cutoff (1%), the M^{pro} E166V TES was identified in 1 additional PAXLOVID-treated subject. In one instance, the E166V substitution co-occurred with an M^{pro} L50F baseline polymorphism. Both the L50F and E166V substitutions have been associated with NIR resistance in cell culture and should be considered RAS. None of these subjects experienced hospitalization or death.
- Several additional M^{pro} TES were identified in PAXLOVID-treated subjects, including T21I, G23D/S/V, C85R/Y, C145F/H, C160R, A173N/T, V186L, D187Y, R188K, T190P, A191P, T199I/P/S, and T304I. In addition, two M^{pro} cleavage site TES were identified in PAXLOVID-treated subjects: M3862I/K and K6796T. It is currently unclear whether any of these TES represent RAS, as they were often identified in both arms and/or at low frequencies. In addition, when the criteria for identifying M^{pro} or M^{pro} cleavage site TES were simply reversed (to identify TES that occurred more frequently in placebo-treated subjects than in PAXLOVID-treated subjects), more M^{pro} and M^{pro} cleavage site TES were found to be enriched in placebo-treated subjects than in PAXLOVID-treated subjects. This finding indicates that some of the TES enriched in PAXLOVID-treated subjects may not be associated with PAXLOVID resistance. However, the T21I and T304I substitutions were associated with NIR resistance in cell culture and should be considered potential RAS.
- In cases of disagreement between the Applicant's frequency table and the FDA's frequency table (e.g., for the M^{pro} P132L/S, V186G, Q189K, A260S/T/V and M^{pro} cleavage site A3571V and A5328P/S TES), most of the differences in results were attributed to substitution frequencies that were above the frequency threshold (10%) in the Applicant's table (~10-30%) but below the threshold in the FDA's table (~1 to 10%). It is currently unclear whether any of these TES represent RAS, as they were often identified in both arms and/or had low frequencies that were not clearly distinguishable from background errors.
- In PAXLOVID-treated subjects, there did not appear to be a significant association between hospitalization or death and baseline M^{pro} polymorphisms at positions of interest, M^{pro} TES associated with PAXLOVID treatment, M^{pro} TES at positions of interest, or M^{pro} cleavage site TES associated with PAXLOVID treatment. Thus, the clinical significance of these substitutions remains unclear.

18.3.5. Updated/Pooled EPIC-HR and EPIC-SR Resistance Analyses

Late in the review cycle the Applicant submitted updated resistance analysis study reports and datasets for the EPIC-HR and EPIC-SR trials. These updated data did not change the overall conclusions from the resistance analyses summarized above. However, in the context of labeling discussions, it was determined that a pooled analysis of the latest available data from the EPIC-HR and EPIC-SR trials would be conducted, and the results of this analysis would be described in Section 12.4 of the prescribing information. As in the analyses described above for the

individual trials, a 10% sensitivity cutoff was used to identify viral M^{pro} or M^{pro} cleavage site amino acid substitutions in each sample. Also consistent with the analyses for the individual trials, the pooled analysis focused on amino acid substitutions that emerged at the same M^{pro} or M^{pro} cleavage site residue in ≥3 PAXLOVID-treated subjects (any change at same position), and at a ≥2-fold greater frequency than in Placebo-treated subjects, across the EPIC-HR and EPIC-SR trials. This algorithm was ultimately used to determine which specific substitutions to describe in the prescribing information.

After censoring subjects from study sites with data anomalies or data reliability concerns, as well as subjects whose "Baseline/Day 1" visit samples were obtained more than 1 hour after the start of study drug dosing (discussed in (Pfizer 2023e)), the pooled analysis was conducted for a total of 907 PAXLOVID recipients and 942 placebo recipients with available baseline and post-baseline sequence analysis data. The following PAXLOVID treatment-emergent substitutions were identified in this analysis:

- M^{pro} substitutions: T98I/R/del (n=4 PAXLOVID [1 EPIC-HR, 3 EPIC-SR], n=0 placebo), E166V (n=3 PAXLOVID [all EPIC-HR], n=0 placebo), and W207L/R/del (n=4 PAXLOVID [2 EPIC-HR, 2 EPIC-SR], n=0 placebo).
- M^{pro} cleavage site substitutions: A5328S/V (n = 7 PAXLOVID [3 EPIC-HR, 4 EPIC-SR], n=1 placebo [EPIC-HR, A5328T]) and S6799A/P/Y (n = 4 PAXLOVID [3 EPIC-HR, 1 EPIC-SR], n = 1 placebo [EPIC-SR, S6799F]).

As discussed above, M^{pro} E166V was the clearest nirmatrelvir resistance-associated TES observed in these analyses. The clinical relevance and potential impact of the other substitutions on nirmatrelvir activity are unclear. Besides M^{pro} E166V, phenotype data are only available for M^{pro} W207L, which did not reduce nirmatrelvir activity in a biochemical assay. Therefore, a post-marketing requirement will be issued for the Applicant to conduct phenotypic analyses of the other noted TES. In addition, while M^{pro} G11V was not identified as a PAXLOVID TES based on this algorithm, any change at this position (C/S/V) was observed in 3 PAXLOVID recipients in EPIC-HR and 1 PAXLOVID recipient (and 3 placebo recipients) in EPIC-SR; only G11V was observed in 2 PAXLOVID recipients. Therefore, the post-marketing requirement will include phenotypic analysis of G11V.

18.4. SARS-CoV-2 Genomic Database Surveillance (Through November 30, 2022)

As a condition for Emergency Use Authorization, the Applicant has been required to provide the FDA with monthly surveillance reports to monitor for circulating and emerging SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Note that the Applicant will be required to conduct similar surveillance activities post-approval (see Section 24.1). These reports also contain listings of all amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites (P5 to P5′ positions), their cumulative counts and frequencies, and their counts and frequencies for each of the three previous months. The latest versions of these reports have been cross-referenced to the NDA and cover sequences deposited in the GISAID EpiCov sequence database through November 30, 2022, and thus contains cumulative polymorphism counts and frequencies, as well as counts and frequencies for sequences deposited in August, September, October, or November 2022. Only complete genome sequences with high coverage were

included in the analysis, resulting in a total of 12,664,696 sequences deposited globally since the beginning of the pandemic. Note that analyses of these sequences are affected by disparities in sequencing coverage across geographic regions and countries.

M^{pro} and M^{pro} Cleavage Site Polymorphisms With Frequencies ≥0.1%

In the Applicant's reports, only 16 M^{pro} amino acid polymorphisms had a cumulative or ≥1 monthly frequency of ≥0.1% (1/1,000) in the GISAID database: G15S, T21I, L30I, T45N, A70T, L75F, K88R, L89F, K90R, V104I, P108S, P132H, T169S, F223L, H246Y, and A260V (Table 208). Some of these polymorphisms are known to be associated with particular SARS-CoV-2 variants, e.g., G15S with Lambda, K90R with Beta, and P132H with Omicron sub-variants. Only the L30I,T169S, and F223L polymorphisms had ≥1 monthly frequency increase of ≥3-fold from August 2022 to November 2022. The L30I polymorphism is primarily associated with the Omicron BQ.1.3 sub-variant. Of these polymorphisms, only T21I and P108S have been associated with NIR resistance in cell culture (in combination with other M^{pro} substitutions, Section 20); in analyses of raw NGS data T21I and L30I each emerged at a low level in 1 PAXLOVID-treated subject in EPIC-HR. In biochemical assays, the M^{pro} G15S, T21I, A70T, L75F, K88R, L89F, K90R, P108S, P132H, T169S, and A260V substitutions did not affect NIR activity (Section 20), while the L30I, T45N, V104I, F223L, and H246Y substitutions have not been tested.

Table 208. SARS-CoV-2 M^{pro} Polymorphisms With Cumulative or Monthly Frequencies ≥0.1%

M^{pro} Polymorphism	Cumulative Freq.	8/2022 Freq.	9/2022 Freq.	10/2022 Freq.	11/2022 Freq.
P132H	45.5%	94.6%	93.8%	94.7%	88.1%
K90R	1.39%	0.55%	0.62%	0.70%	0.80%
L89F	1.15%	0.17%	0.14%	0.24%	0.28%
T169S	0.48%	0.07%	0.01%	0.18%	0.01%
P108S	0.22%	0.16%	0.12%	0.10%	0.23%
A260V	0.20%	0.04%	0.06%	0.06%	0.09%
G15S	0.18%	0.02%	0.03%	0.05%	0.04%
L75F	0.15%	0.21%	0.18%	0.18%	0.13%
K88R	0.15%	0.03%	0.05%	0.05%	0.05%
T21I	0.13%	0.10%	0.14%	0.15%	0.14%
H246Y	0.06%	0.15%	0.16%	0.15%	0.16%
T45N	0.03%	0.14%	0.16%	0.19%	0.30%
A70T	0.02%	0.11%	0.04%	0.05%	0.03%
F223L	0.02%	0.01%	0.02%	0.05%	0.26%
V104I	0.02%	0.02%	0.03%	0.05%	0.12%
L30I	0.01%	<0.01%	0.01%	0.10%	0.35%

Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Abbreviations: Freq, frequency; M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In the Applicant's report, only 7 M^{pro} cleavage site polymorphisms had a cumulative or ≥1 monthly frequency of ≥0.1% (1/1,000) in the GISAID database: A3571V, R3574K, V3855I, T4249I, A5922S/V, and T5923I (Table 209). Only the R3574K and V3855I polymorphisms increased in frequency ≥3-fold from October 2022 to November 2022. Note that A3571V emerged in 3 PAXLOVID-treated subjects in EPIC-HR, but also in 1 or 2 placebo-treated subjects (depending on analysis). None of these changes have been associated with NIR resistance in cell culture, and their impact on NIR activity has not been determined.

Table 209. SARS-CoV-2 M^{pro} Cleavage Site Polymorphisms With Cumulative or Monthly Frequencies ≥0.1%

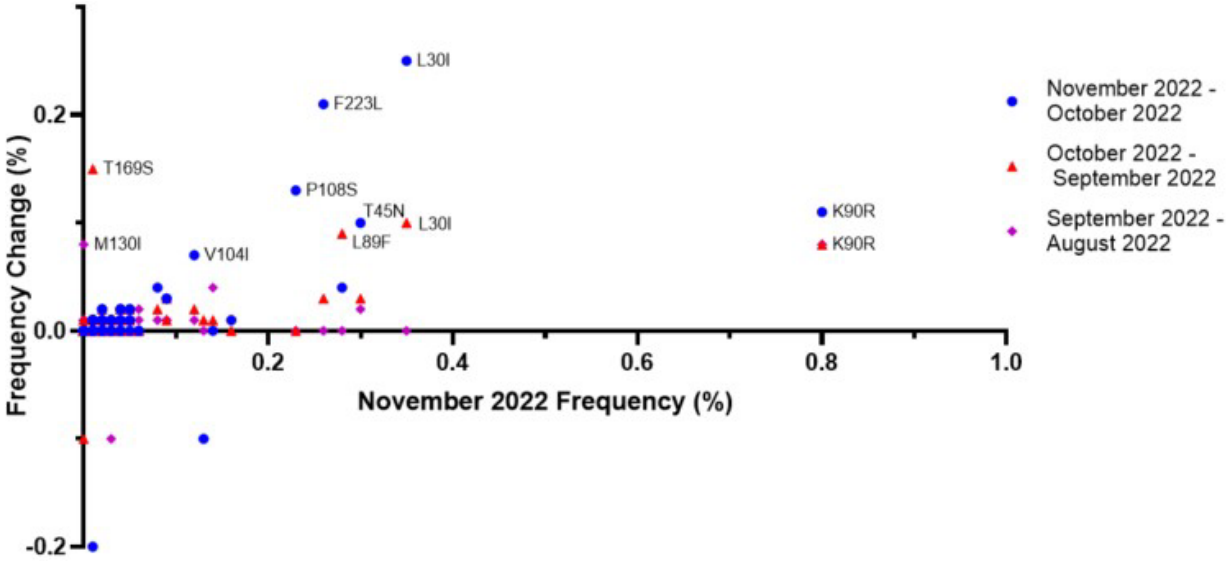
pp1ab Polymorphism	CS	CS Position	Cumulative Freq.	10/2022 Freq.	11/2022 Freq.
A3571V	nsp5/nsp6	P2′	0.50%	0.05%	0.08%
A5922S	nsp13/nsp14	P4	0.24%	0.02%	0.03%
T5923I	nsp13/nsp14	P3	0.13%	0.08%	0.09%
T4249I	nsp9/nsp10	P5	0.13%	0.12%	0.12%
A5922V	nsp13/nsp14	P4	0.10%	0.05%	0.07%
R3574K	nsp5/nsp6	P5′	0.03%	0.04%	0.16%
V3855I	nsp6/nsp7	P5	0.01%	0.07%	0.31%

Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Abbreviations: CS, cleavage site; Freq, frequency; M^{pro}, main protease; nsp, nonstructural protein; P, position; pp, polyprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

M^{pro} and M^{pro} Cleavage Site Polymorphisms With Recent Increases in Frequencies

To identify emerging M^{pro} polymorphisms, the frequency of each M^{pro} polymorphism in November 2022 was plotted against the absolute change in polymorphism frequency from August 2022 through November 2022 (Figure 88). The M^{pro} polymorphisms with the greatest increases in absolute frequencies (at least 1 monthly increase of ≥0.05%) were L30I, T45N, L89F, K90R, V104I, P108S, M130I, P132H, T169S, and F223L. Of these polymorphisms, only P108S has been associated with NIR resistance in cell culture (in combination with other M^{pro} substitutions, Section 20). In biochemical assays, the M^{pro} L89F, K90R, P108S, P132H, and T169S substitutions did not affect NIR activity (Section 20), while the L30I, T45N, V104I, M130I, and F223L substitutions have not been tested.

Figure 88. Changes in SARS-CoV-2 M^{pro} Polymorphism Frequencies From August 2022 Through November 2022



Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Note: The x-axis indicates the M^{pro} polymorphism frequency (%) in November 2022, while the y-axis indicates the absolute change in M^{pro} polymorphism frequency (%) between the indicated months. The M^{pro} P132H polymorphism is not shown.
Abbreviations: M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

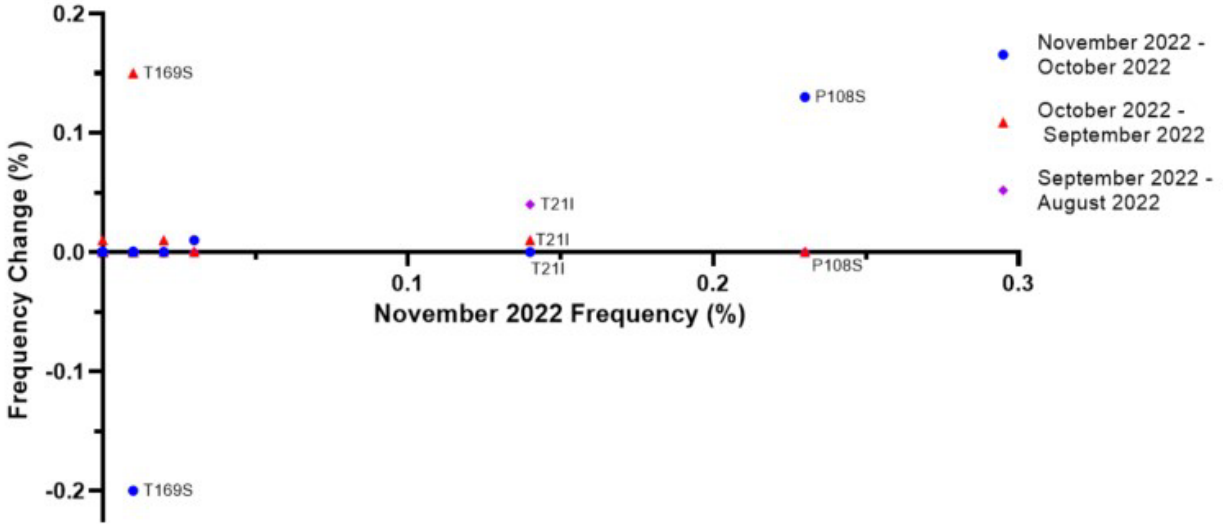
To identify emerging M^{pro} cleavage site polymorphisms, the frequency of each M^{pro} cleavage site polymorphism in November 2022 was compared to its cumulative frequency and frequency in

October 2022. Only two M^{pro} cleavage site polymorphisms had a frequency in November 2022 that was at least 0.05% greater than its cumulative frequency or frequency in October 2022: V3855I and R3574K (Table 209). These substitutions have not been associated with NIR resistance in cell culture, and their impact on NIR activity has not been determined.

M^{pro} Polymorphism Frequencies at 34 Positions of Interest

Lastly, M^{pro} polymorphism frequencies were analyzed at 34 residues that are considered positions of interest (Table 202), including 23 residues that directly contact or are located in close proximity (<5 Å) of NIR and 11 additional residues that have been associated with NIR resistance in cell culture. The most common polymorphisms at these positions in November 2022 sequences were T21I and P108S (Figure 89). The T21I polymorphism increased in frequency from August 2022 to September 2022, but subsequently did not change much in frequency. Conversely, the P108S polymorphism only increased in frequency from October 2022 to November 2022. The T169S polymorphism increased in frequency from September 2022 to October 2022 but subsequently decreased in frequency from October 2022 to November 2022. The T21I and P108S polymorphisms have both been associated with NIR resistance in cell culture (in combination with other substitutions) but did not affect NIR activity in a biochemical assay (Section 20). The E166V polymorphism was observed in only 9 of ~12.7 million sequences.

Figure 89. Changes in SARS-CoV-2 M^{pro} Polymorphism Frequencies at Positions of Interest From August 2022 Through November 2022



Source: FDA analysis of 10/2022 and 11/2022 surveillance reports.
Note: The x-axis indicates the M^{pro} polymorphism frequency (%) at 34 positions of interest in November 2022, while the y-axis indicates the absolute change in M^{pro} polymorphism frequency (%) between the indicated months.
Abbreviations: M^{pro}, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

18.5. Investigation of Clinical Virology Data Anomalies

During the review we identified certain unusual patterns of viral RNA levels and viral sequencing results at selected study sites in EPIC-HR and EPIC-SR. In at least one of these sites

highly unusual patterns of symptom data collection were also observed in some of the same subjects with unusual viral RNA patterns. These observations triggered additional site inspections and in-depth investigation of all study data and sites from EPIC-HR and EPIC-SR.

18.5.1. Observations of Viral RNA and Sequencing Anomalies at Specific Study Sites

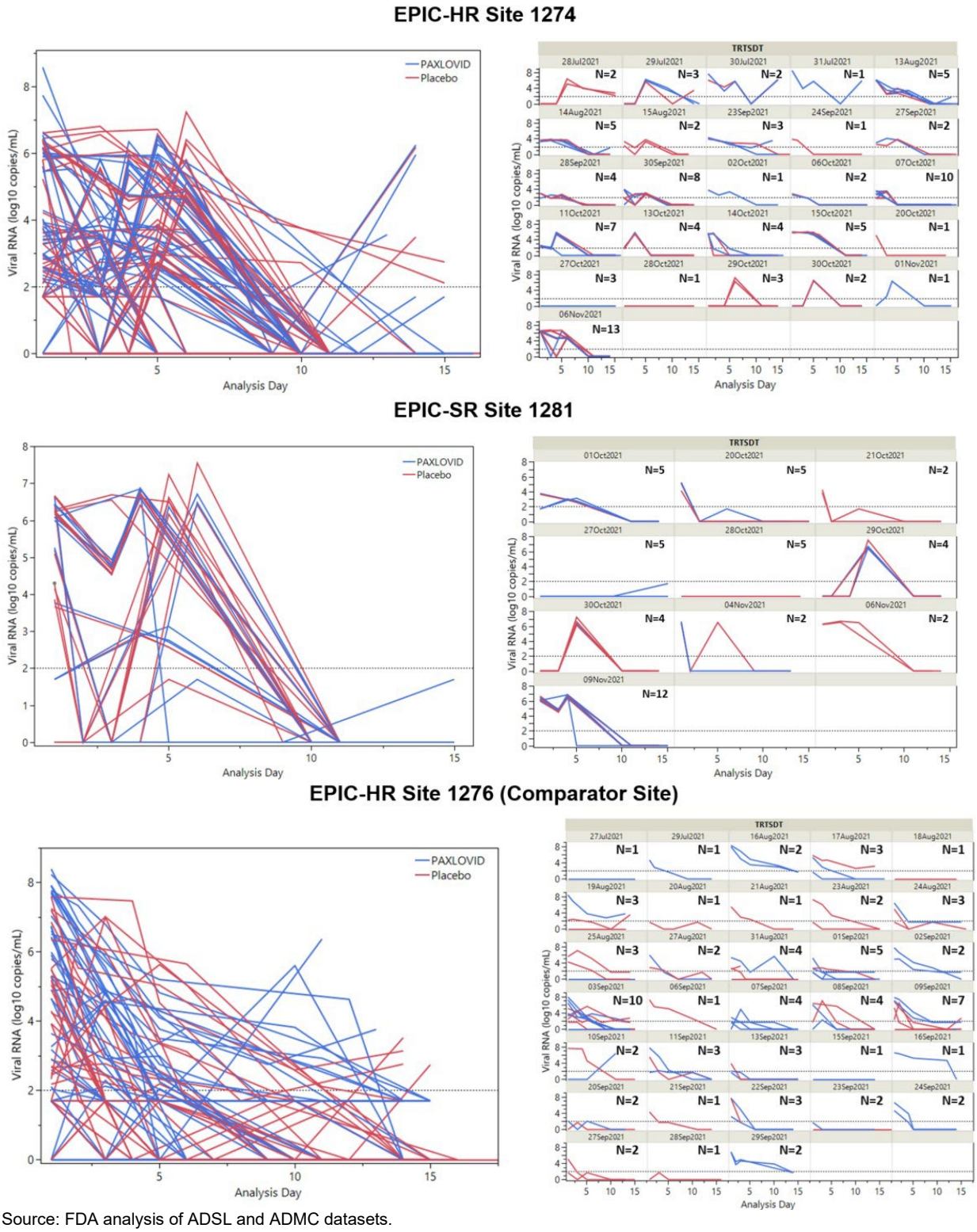
Unusual patterns of viral RNA levels in NP samples over time were observed among subjects at the following study sites:

- EPIC-HR: Site 1274 (Principal investigator [PI]: Gonzalez/Martinez, Cutler Bay, FL, USA; same location as EPIC-SR site 1281)
- EPIC-SR: Site 1281 (PI: Gonzalez/Martinez, Cutler Bay, FL, USA; same location as EPIC-HR site 1274), Site 1157 (PI: Medzhidiev, Sofia, Bulgaria), and Site 1197 (PI: Haytova, Vratsa, Bulgaria, 2022 enrollment period)

The unusual viral RNA patterns were characterized by a high degree of overlapping and often implausible trends in viral RNA shedding levels over time in different subjects at the same site, which in many cases were associated with similar timing of treatment initiation (Figure 90, Figure 91, Figure 92, and Figure 93, FDA analyses). For example, in EPIC-HR Site 1274, 4 different subjects who all started treatment on October 13, 2021, (2 received PAXLOVID, 2 received placebo) had a similar major spike in viral RNA levels between the Baseline and the Day 3 visits, and in all subjects viral RNA declined to undetected levels at all subsequent visits. As another example from EPIC-HR Site 1274, 5 subjects who started treatment on October 15, 2021, (3 received PAXLOVID, 2 received placebo) all had highly similar viral RNA levels which had a relatively delayed decline over time.

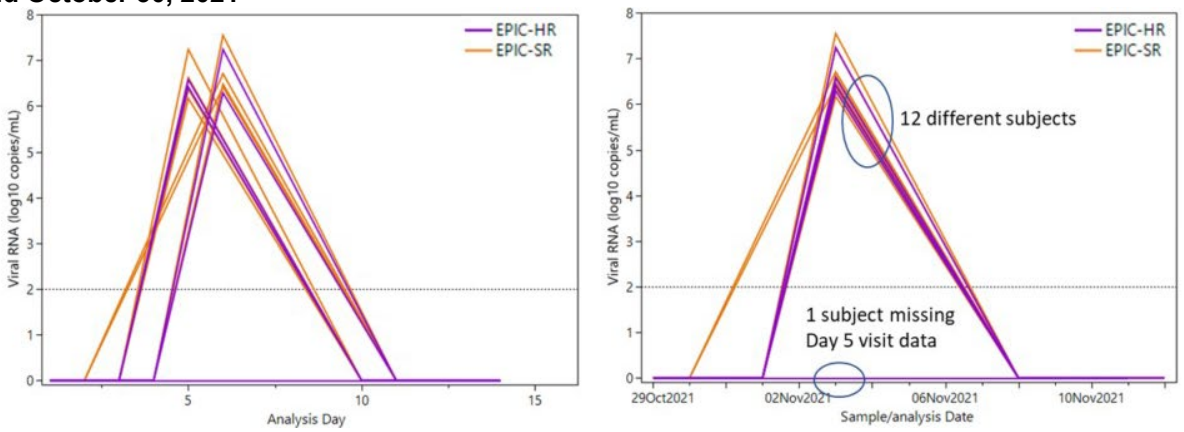
The overlapping viral RNA patterns within the Gonzalez/Martinez site (EPIC-HR Site 1274/EPIC-SR Site 1281) extended between both trials. For example, 12 different subjects across both trials who initiated treatment on October 29, 2021, or October 30, 2021, had highly similar patterns of viral RNA over time, with viral RNA levels of 6.2 to 7.6 $\log_{10}$ copies in the Day 5 visit window, which corresponded to actual analysis Days 5 or 6 (Figure 91). At all other study visits for all 12 subjects, including the Baseline visit, viral RNA levels were reported as target not detected. One additional subject who started treatment on October 29, 2021, had viral RNA target not detected at all study visits, and the subject was missing data for the Day 5 visit when the other 12 subjects had the characteristic spike in viral RNA. The viral RNA peak in the 12 subjects was staggered by 1 Analysis Day (i.e., day relative to start of treatment), although for all 12 subjects the viral RNA sampling actually occurred on the same exact date (November 3, 2021) within a ~4-hour window. These and other viral RNA patterns from this site are highly implausible and raise concerns about virology data quality or data integrity.

Figure 90. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Martinez), or EPIC-HR Site 1276 (Comparator Site)



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid; TRTSDT, treatment start date

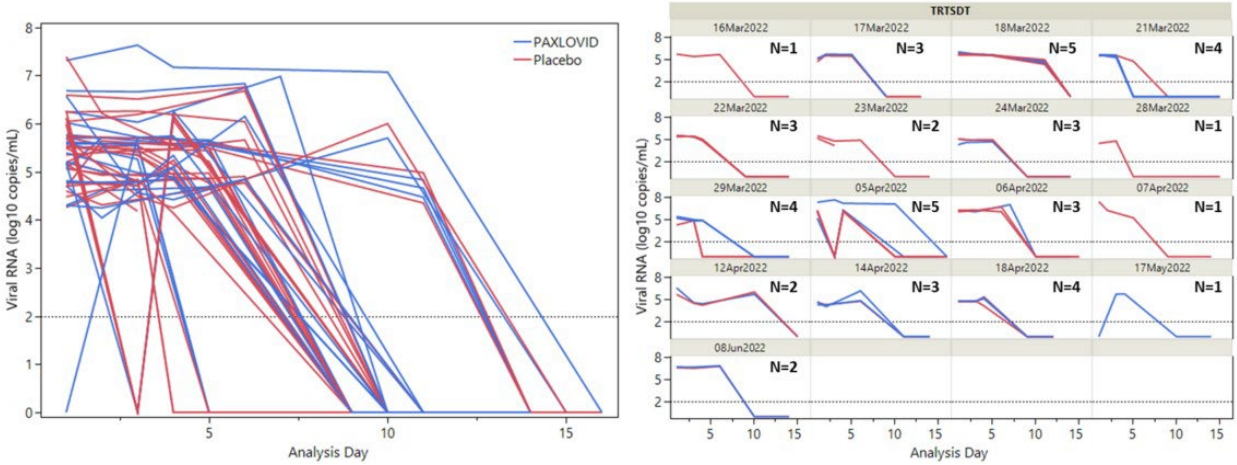
Figure 91. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-HR 1274/EPIC-SR 1281 Sites (PI: Gonzalez/Martinez) With Treatment Start Dates of October 29, 2021 and October 30, 2021



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

Unusual patterns of overlapping viral RNA levels over time were also observed in EPIC-SR site 1157 (PI: Medzhidiev, Bulgaria) (Figure 92). As in EPIC-HR 1274/EPIC-SR 1281, the viral RNA patterns clustered largely by treatment start date.

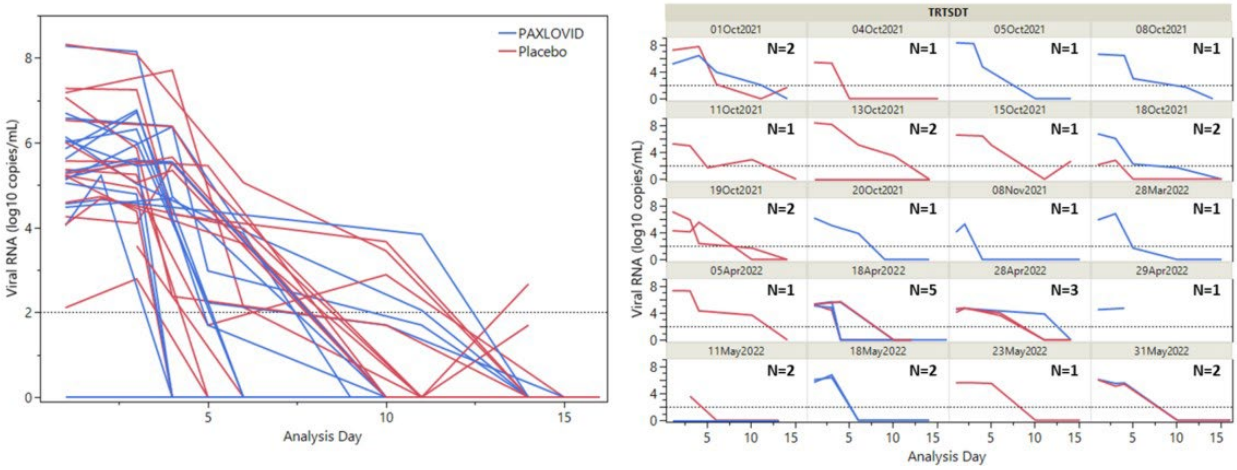
Figure 92. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-SR Site 1157 (PI: Medzhidiev)



Source: FDA analysis of ADSL and ADMC datasets.
Note: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

Unusual viral RNA patterns, again clustered by treatment start date, were also observed at a second EPIC-SR site in Bulgaria, site 1197 (PI: Haytova) (Figure 93). The overlapping viral RNA patterns at this site were not as striking as the other sites noted above and appeared to be restricted to the 2022 enrollment period (i.e., Omicron infections). Note that the same PI enrolled subjects in EPIC-HR as site 1193, and analyses of viral RNA levels from these subjects did not identify evidence of overlapping patterns of viral RNA over time, either overall or grouped by treatment start date (analyses not shown).

Figure 93. Viral RNA Levels in NP Swab Samples From Subjects Who Enrolled at EPIC-SR Site 1197 (PI: Haytova)

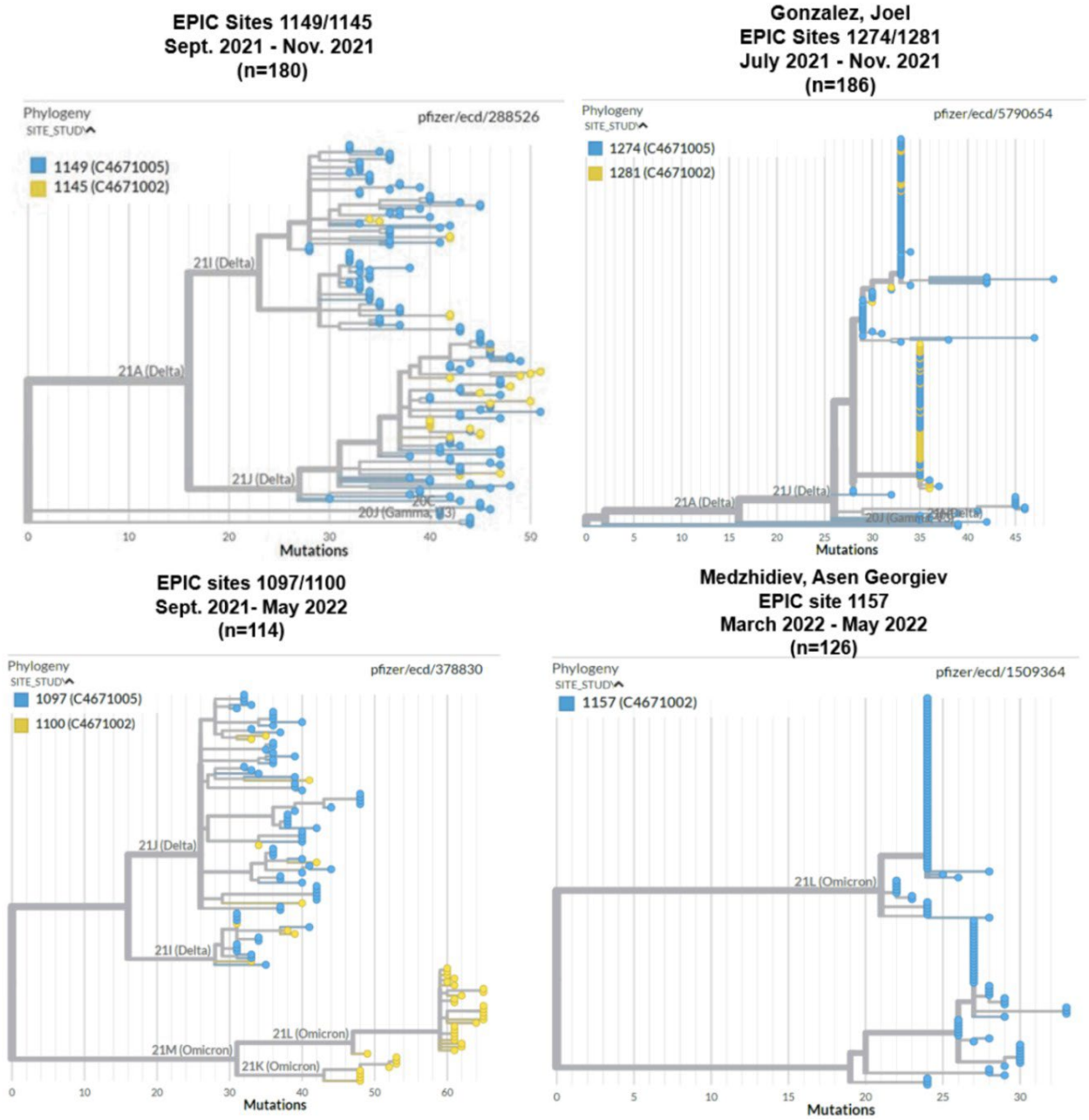


Source: FDA analysis of ADSL and ADMC datasets.
Notes: Dashed lines indicate qRT-PCR assay LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; log, logarithm; N, total number of subjects; qRT-PCR, real-time, quantitative, reverse transcription-polymerase chain reaction; RNA, ribonucleic acid

The same viral RNA samples used for qRT-PCR analyses were also subjected to next generation sequencing analyses to support resistance analyses and identification of SARS-CoV-2 variants. Following the observations of overlapping viral RNA patterns noted above, extensive analyses of viral sequences were conducted by the Applicant and FDA to assess for unusual patterns of genetic clustering, which could indicate flawed or improper sample handling or processing. Independent FDA analyses were conducted using CLC genomics software. These analyses were conducted on consensus nucleotide sequences spanning the entire ~30 kb SARS-CoV-2 genome.

As shown in Figure 94, phylogenetic analyses of viral consensus nucleotide sequences conducted by the Applicant indicated extensive genetic clustering of numerous viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site, as well as from the EPIC-SR site 1157, with many sequences having minimal to nonexistent branch lengths indicating nearly or completely identical viral nucleotide sequences. This extent of viral genetic conservation across different subjects is implausible and strongly indicates flawed NP swab sample collection, handling, or processing from these sites.

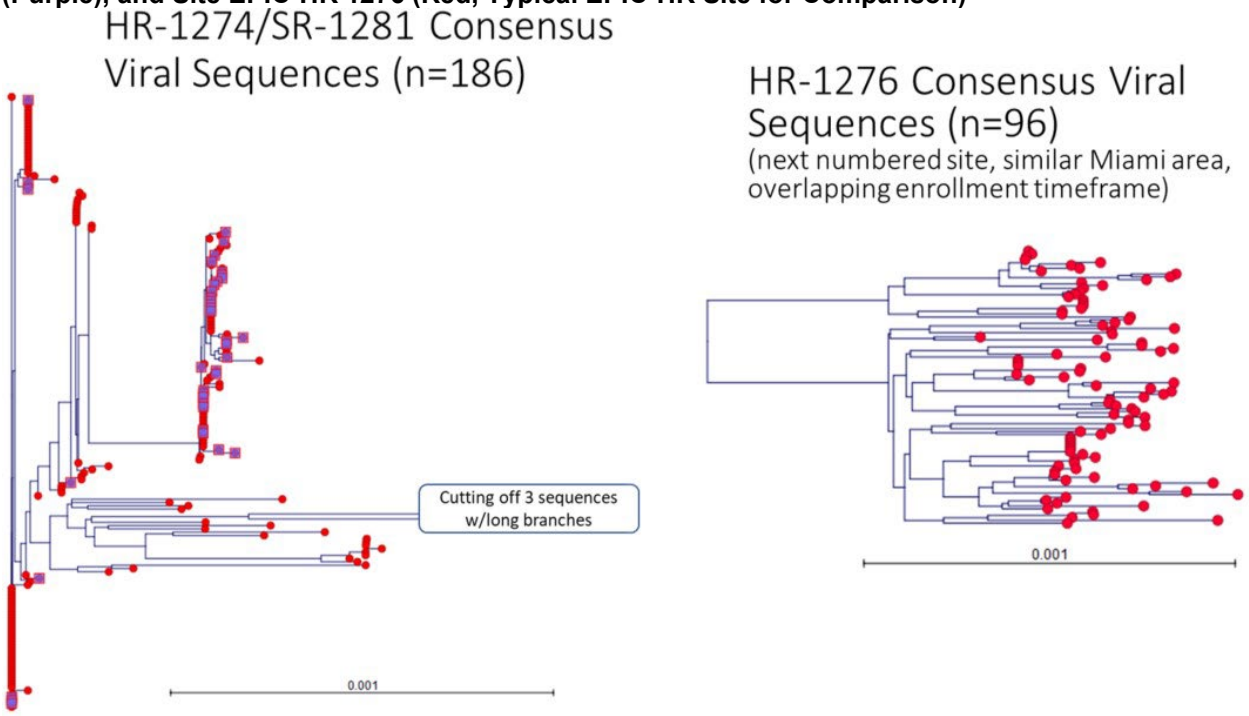
Figure 94. Nextstrain Phylogenetic Analysis of Viral Sequences From the EPIC-HR 1274/EPIC-SR 1281 site, EPIC-SR Site 1157, and Comparator Sites



Source: (Pfizer 2022p).
Abbreviations: n, number of subjects in sample

Independent FDA analyses confirmed the extensive clustering of viral sequences from different subjects from the EPIC-HR 1274/EPIC-SR 1281 site (Figure 95).

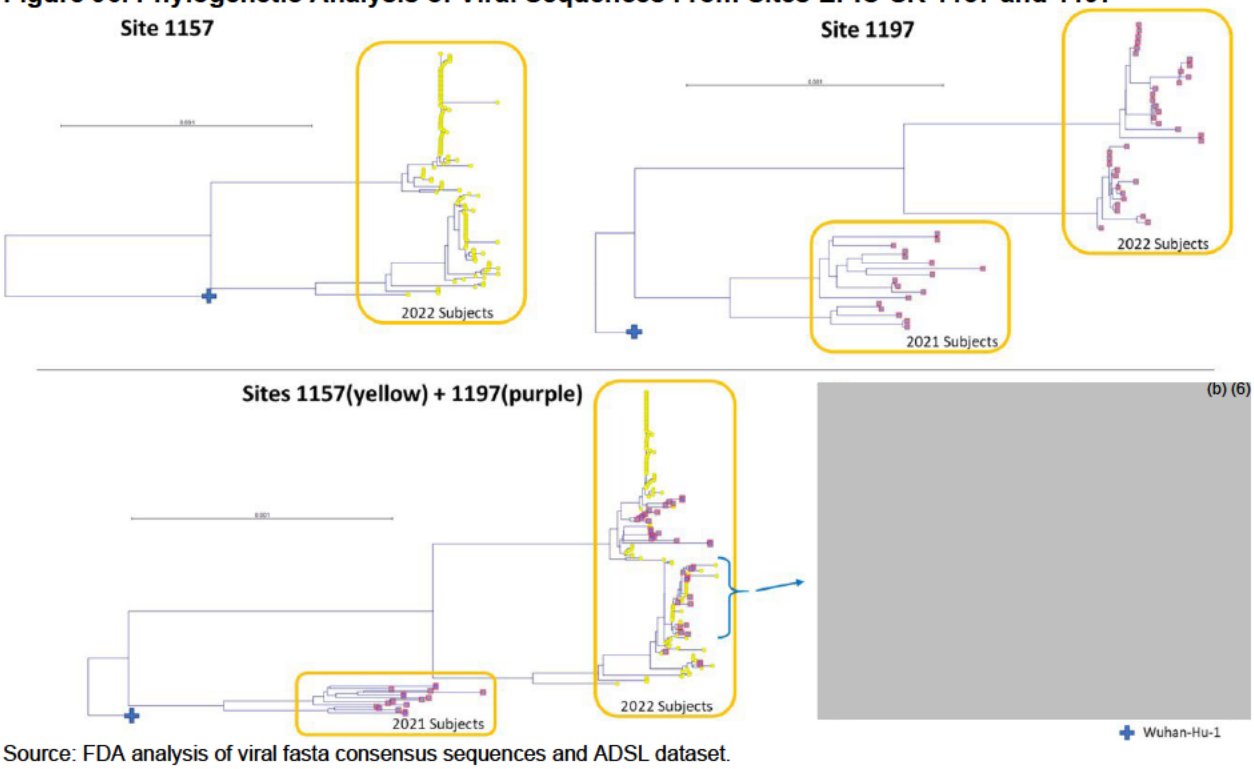
Figure 95. Phylogenetic Analysis of Viral Sequences From Site EPIC-HR 1274 (Red)/EPIC-SR 1281 (Purple), and Site EPIC-HR 1276 (Red, Typical EPIC-HR Site for Comparison)



Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.
Abbreviations: n, number of subjects in sample; w/, with

Independent FDA analyses also confirmed extensive clustering of viral sequences from EPIC-SR site 1157 in Bulgaria (Figure 96). Clustering of viral sequences from site 1197 (also in Bulgaria) was not as clear as in site 1157, but for subjects who enrolled in the 2022 period (among whom anomalous viral RNA patterns were observed) there is some evidence of clustering of viral sequences with short or no branch lengths. Furthermore, combined phylogenetic analyses of viral sequences from EPIC-SR sites 1157 and 1197 revealed a cluster of closely matched sequences from both sites, including 2 site 1197 samples ((b) (6) Days 1/5) that were 100% identical with a large cluster of identical sequences from site 1157, and a third sample from 1197 ((b) (6) Day 1) being 100% identical to sequences from two other subjects from site 1157 (Day 3, (b) (6) Day 5). The fact that both sites are located in the same country could account for some genetic clustering of viral sequences, although this extent of genetic clustering between sites was not as apparent in phylogenetic analyses combining sequences from site 1197 with those from the other 21 EPIC-SR sites in Bulgaria (data not shown).

Figure 96. Phylogenetic Analysis of Viral Sequences From Sites EPIC-SR 1157 and 1197



Source: FDA analysis of viral fasta consensus sequences and ADSL dataset.

18.5.2. Expanded Investigations of All Study Sites for Viral RNA or Sequencing Anomalies

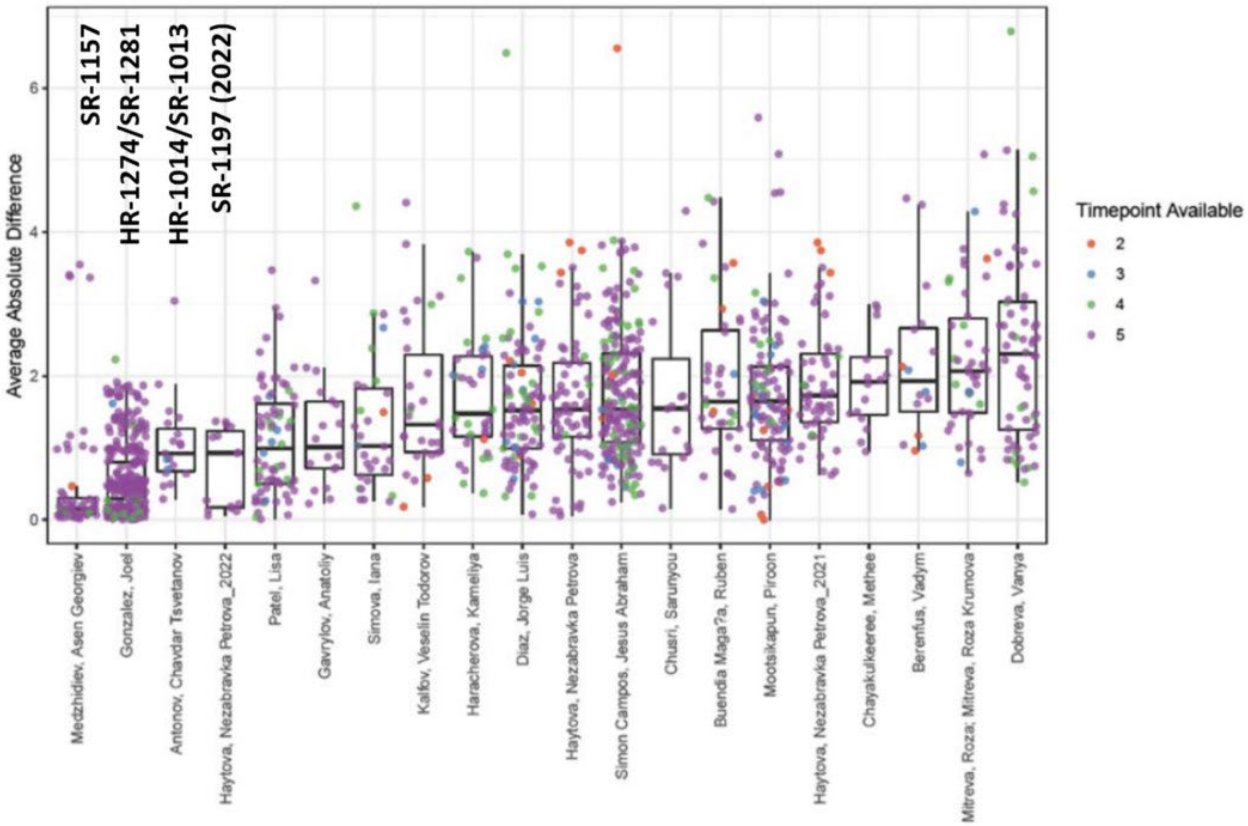
Numerous additional analyses were conducted by the Applicant and FDA to assess for viral RNA or sequencing anomalies across all study sites in EPIC-HR and EPIC-SR, and ultimately to ensure reliability of these data after censoring data from the concerning sites discussed above. Note that across different sites there was a wide range in the numbers of subjects with unquantifiable or undetected viral RNA at baseline or throughout the study period, which was at least partially associated with baseline serostatus (discussed below), and viral sequence data would only be available for samples with sufficient viral RNA. Therefore, these analyses for viral RNA or sequencing anomalies were necessarily biased towards sites with sufficient numbers of subjects with quantifiable viral RNA and available viral sequencing data.

In somewhat subjective analyses, viral RNA patterns within individual study sites with viral RNA data from ≥10 subjects were assessed visually by FDA for evidence of overlapping trends between subjects, both overall and also grouped by treatment start date, as described above. While some degree of overlapping viral RNA patterns between small numbers of subjects was observed and was expected by chance alone, no additional sites beyond those noted above had such clear patterns of overlapping viral RNA levels over time between different subjects, particularly between those with the same or similar treatment start dates.

In a more quantitative assessment, the Applicant conducted an analysis of "longitudinal viral RNA level profile similarity" between pairs of participants with the same treatment start date. These analyses considered sites across both EPIC-HR and EPIC-SR with ≥15 subjects, but the analyses excluded sites from India due to low average baseline viral RNA levels, as well as

participants with viral RNA levels <LLOQ across all study visits. As shown in Figure 97, and consistent with the viral RNA patterns noted above, EPIC-SR 1157 and EPIC-HR 1274/EPIC-SR 1281 were clear outliers based on the relatively low differences in $\log_{10}$ viral RNA levels between participants with the same treatment start date. The median difference shown for EPIC-SR 1197 (2022) was similar to multiple other sites, although there was a group of data points showing minimal differences in viral RNA levels between a subset of participants with the same treatment start date. Site EPIC-HR 1014/EPIC-SR 1013 had a relatively low median difference in this analysis, but the median was similar to multiple other sites, and no data points clustered near 0, indicating no two subjects with the same treatment start date had highly overlapping viral RNA patterns. Visual analysis of viral RNA results from this EPIC-HR 1014/EPIC SR-1013 indicated some similar viral RNA patterns between different subjects, but not to the same extent as the other sites, and not tightly associated with treatment start date. Overall, this analysis confirms the observations of overlapping viral RNA patterns noted above for sites EPIC-HR 1274/EPIC-SR 1281, EPIC-SR 1157 and EPIC-SR 1197 (2022 enrollment period), and no other sites with similar patterns were identified.

Figure 97. Applicant's Analysis of Average Absolute Difference in Log10 Viral RNA Level Across Timepoints Between Participants With the Same Treatment Start Day, Grouped by EPIC-HR and EPIC-SR Investigators



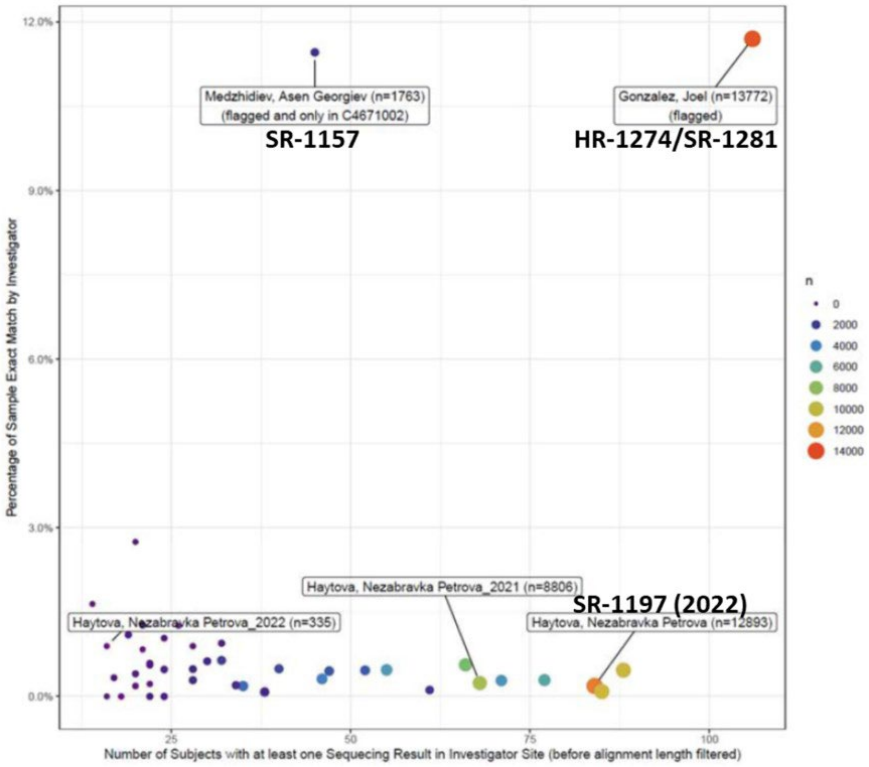
Source: (Pfizer 2022p) (modified to include site numbers).
Abbreviations: log, logarithm; RNA, ribonucleic acid

The Applicant conducted nucleotide basic local alignment search tool (BLASTN) analyses of full-length viral genome consensus nucleotide sequences to measure viral genome similarity between all pairs of samples from different participants within each investigator site (NCBI

Reference ID: 5179402

2023). This analysis calculated the numbers of nucleotide mismatches between sequences across the full viral genome. Results from each site were summarized by the percentage of sample comparisons between different participants that yielded an exact match (mismatch count = 0). The rationale for this analysis was that different visit samples from the same participant might match exactly; however, samples from different participants should rarely match exactly at the nucleotide level, and thus a high number of matching sequences between different subjects would indicate contaminating sequences or otherwise implausible concordance of viral sequences due to mishandling of virology samples or another potential technical problem. The analysis was conducted for investigator sites (excluding sites from India, as described previously) with numbers of sample comparisons ≥300. As shown in Figure 98, EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) were again clear outliers based on having relatively high numbers of samples between participants within these sites with exactly matching viral nucleotide sequences. No other sites, including EPIC-SR 1197 (2022, Haytova), were identified in this analysis for having an unusually high percentage of samples with exactly matching viral nucleotide sequences.

Figure 98. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences for Exact Matches of Sequences Between Different Subjects at the Same Site



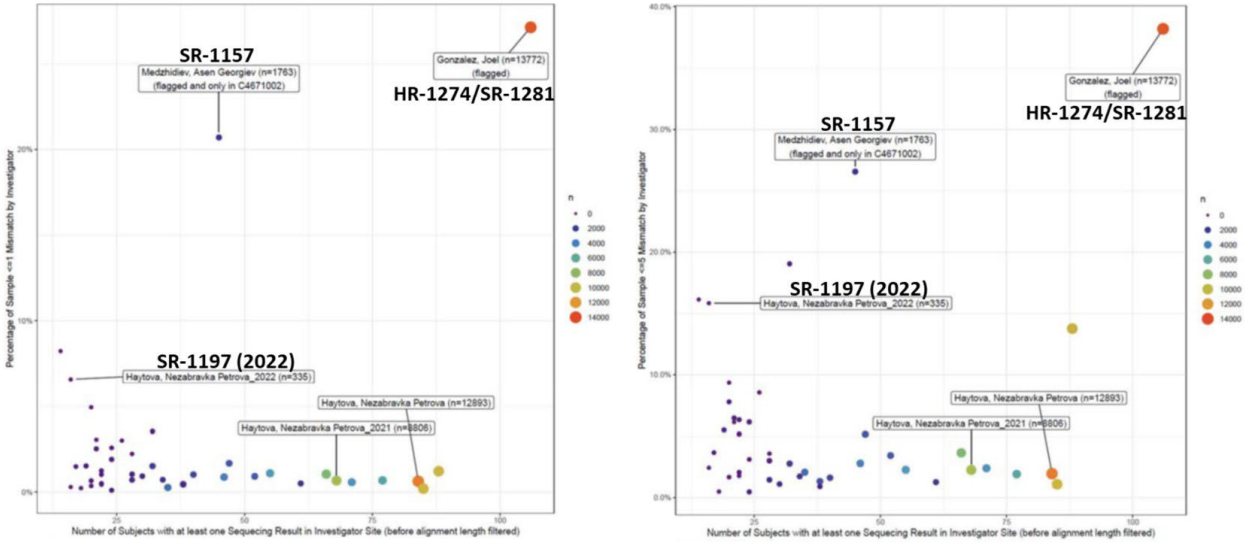
Source: (Pfizer 2022p) (modified to include site numbers).
Note: Shown are the percentages of samples with exact sequence matches between pairs of samples from different participants for sites with ≥300 sequence pairs.
Abbreviations: BLASTN, nucleotide basic local alignment search tool; n, number of paired sequence comparisons

Given the length of the viral genome (~30 kb) and the expectation that any SARS-CoV-2 clinical specimen would have a mixture of co-existing viral sequences, if the same exact specimen were processed and sequenced in two independent analyses it would not be surprising to observe a small number of nucleotide differences between the consensus viral nucleotide sequences

Reference ID: 5179402

generated from the two replicates. Therefore, the requirement for exactly matching viral nucleotide sequences in the BLASTN analysis above could be too stringent to identify pairs of highly similar viral sequences from different subjects that might indicate technical mishandling of samples. To address this limitation, we requested that the Applicant repeat the BLASTN analysis identifying similar sequences based on different stringencies of sequence mismatches (≤1, ≤5 or ≤10 mismatches). As shown in Figure 99, when the analysis was repeated to identify sequences with ≤1 or ≤5 mismatches, the EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) sites remained the outliers, while the data from SR-1197 (2022, Haytova) showed an increasing signal in the percentages of samples with highly similar viral sequences, consistent with the short branch lengths observed in the phylogenetic analyses from this site (summarized above). Nevertheless, the signal from SR-1197 (2022, Haytova) was not as obvious as those from EPIC-SR 1157 (Medzhidiev) and EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez). The BLASTN analyses allowing for ≤10 mismatches were found to be insufficiently stringent as much larger percentages of samples across several sites were identified as having similar sequences, likely reflecting natural sequence similarities within local geographic regions.

Figure 99. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences to Identify Highly Similar Sequences Between Different Subjects at the Same Site

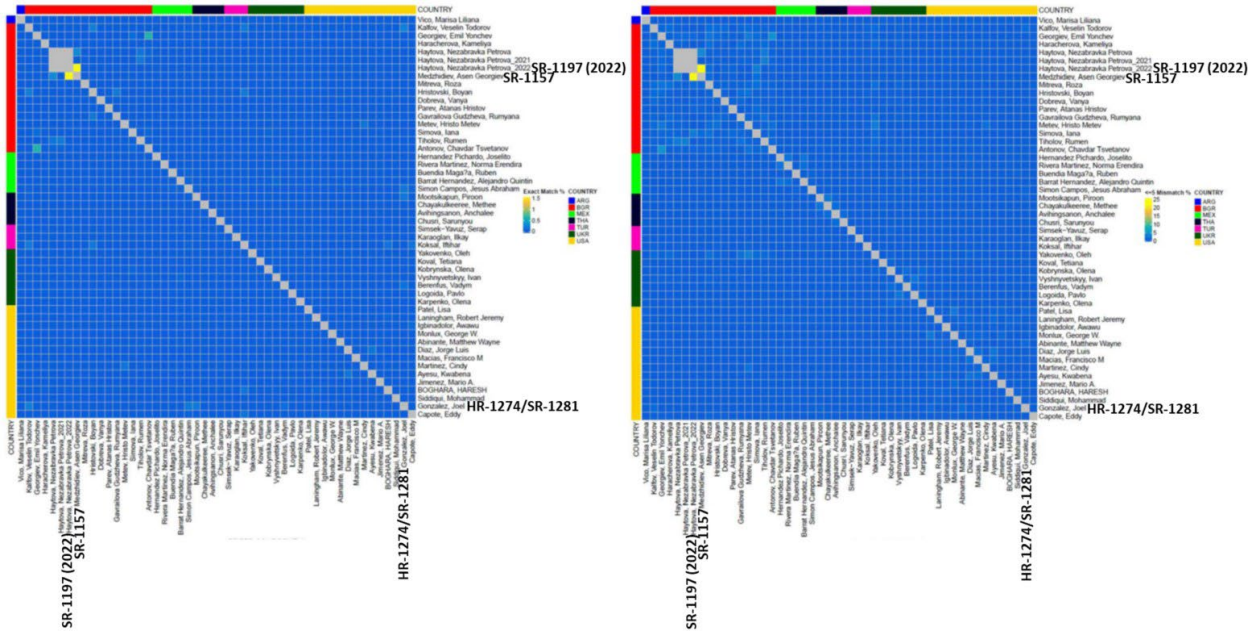


Source: (Pfizer 2022p) (modified to include site numbers).
Note: Shown are the percentages of samples with ≤1 (left) or ≤5 (right) mismatches between pairs of samples from different participants for sites with ≥300 sequence pairs.
Abbreviations: BLASTN, nucleotide basic local alignment search tool; n, number of nucleotide matches

The Applicant also conducted additional BLASTN analyses to identify instances of identical or nearly identical viral consensus nucleotide sequences between subjects from different investigator sites. These analyses were restricted to sites with at least 15 subjects with available sequencing results, and again different levels of allowed mismatches between sequences (0 [i.e., exact], ≤1, ≤5 and ≤10) were considered. Figure 100 shows heatmaps of results from the analyses of identical (0 mismatches) and nearly identical (≤5 mismatches) sequences between study sites, illustrating that EPIC-SR Sites 1157 (Medzhidiev) and 1197 (Haytova, 2022) were the only sites that showed a signal of similar sequences between subjects from different study sites. No other sites even within Bulgaria or any other country showed a similar degree of nearly

identical viral sequences between subjects from different sites. These results are consistent with the phylogenetic analyses summarized above that show clustering of viral nucleotide sequences between EPIC-SR Sites 1157 (Medzhidiev) and 1197 (Haytova, 2022).

Figure 100. BLASTN Analysis of Consensus Full-Length Viral Nucleotide Sequences to Identify Highly Similar Sequences Between Different Subjects at Different Study Sites



Source: (Pfizer 2022q) (modified to include site numbers).
Note: Shown are heatmaps illustrating the percentages of samples with exact sequences (left) or ≤5 mismatches (right) between samples from two different sites, restricted to investigators with ≥15 subjects.
Abbreviations: ARG, Argentina; BRG, Bulgaria; BLASTN, nucleotide basic local alignment search tool; MEX, Mexico; n, number of nucleotide matches; THA, Thailand; TUR, Turkey; UKR, Ukraine; USA, United States of America

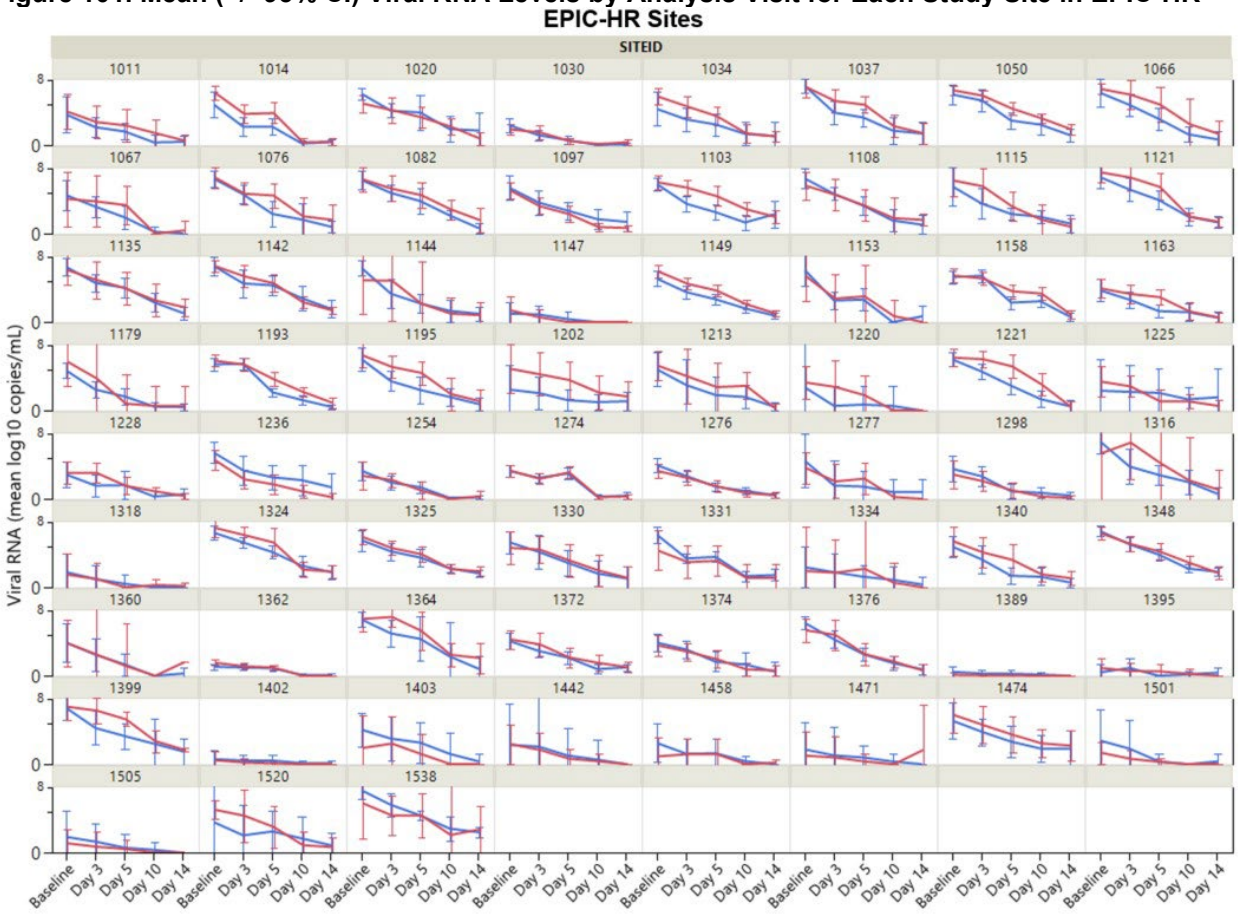
Extensive additional phylogenetic analyses were conducted by both FDA and the Applicant (data not shown), and these analyses did not identify any unusual patterns of viral genetic clustering between sequences from different subjects either within or between study sites, beyond the observations summarized above.

18.5.3. Study Sites with High Frequencies of Undetected Viral RNA

As noted above, while conducting these analyses we found that across different study sites there was a wide range in the numbers of subjects with low or undetected viral RNA at baseline or throughout the study period. Figure 101 and Figure 102 show the mean viral RNA levels at each study visit for each study site with viral RNA data from ≥10 subjects.

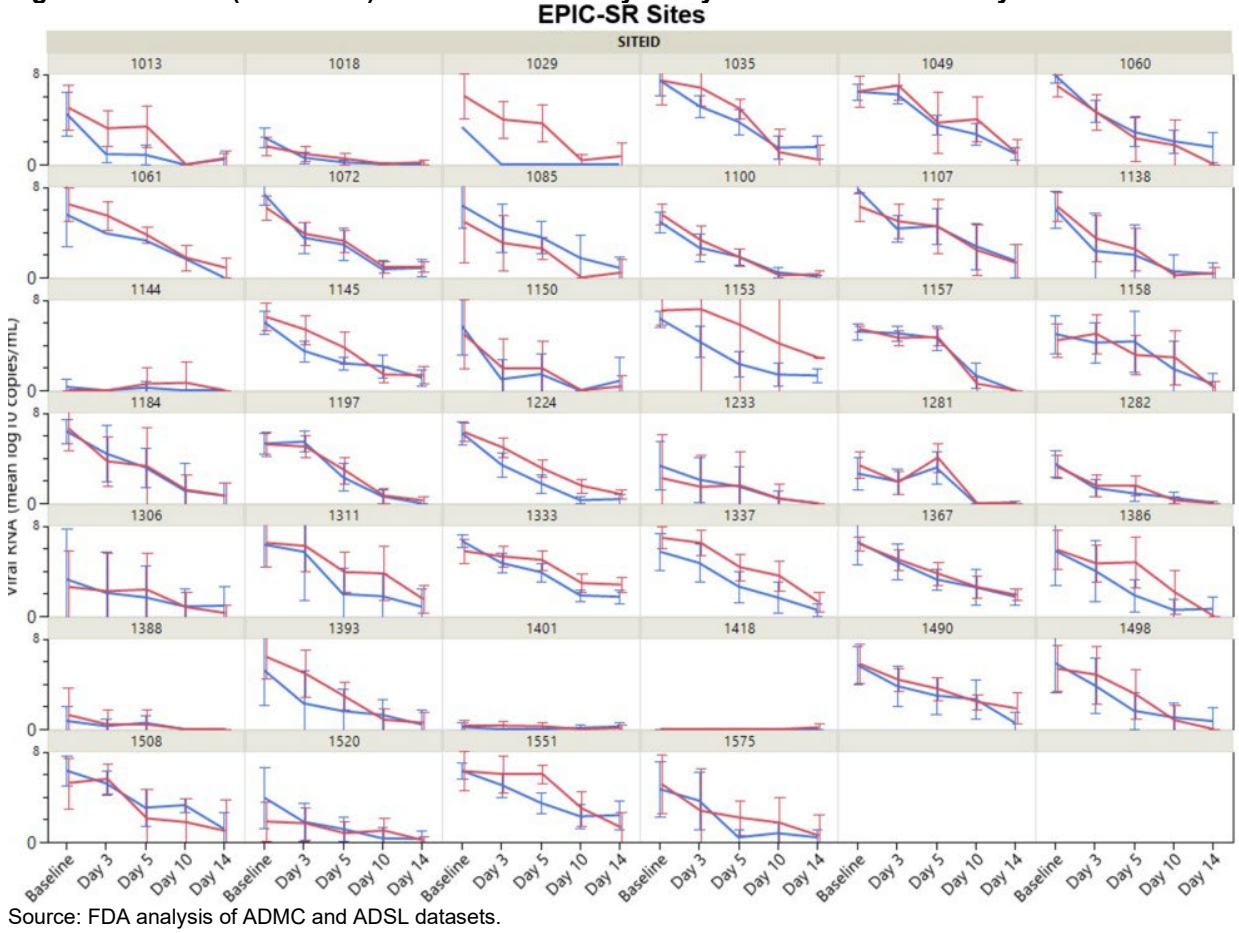
Reference ID: 5179402

Figure 101. Mean (+/- 95% CI) Viral RNA Levels by Analysis Visit for Each Study Site in EPIC-HR



Source: FDA analysis of ADMC and ADSL datasets.
Note: Blue: PAXLOVID-treated subjects. Red: Placebo-treated subjects.
Note: Viral RNA results of detected/<LLOQ were assigned a value of 1.7 $\log_{10}$ copies/mL, and results of undetected RNA were assigned a value of 0 copies/mL.
Note: Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: CI, confidence interval; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SITEID, site identifier

Figure 102. Mean (+/- 95% CI) Viral RNA Levels by Analysis Visit for Each Study Site in EPIC-SR

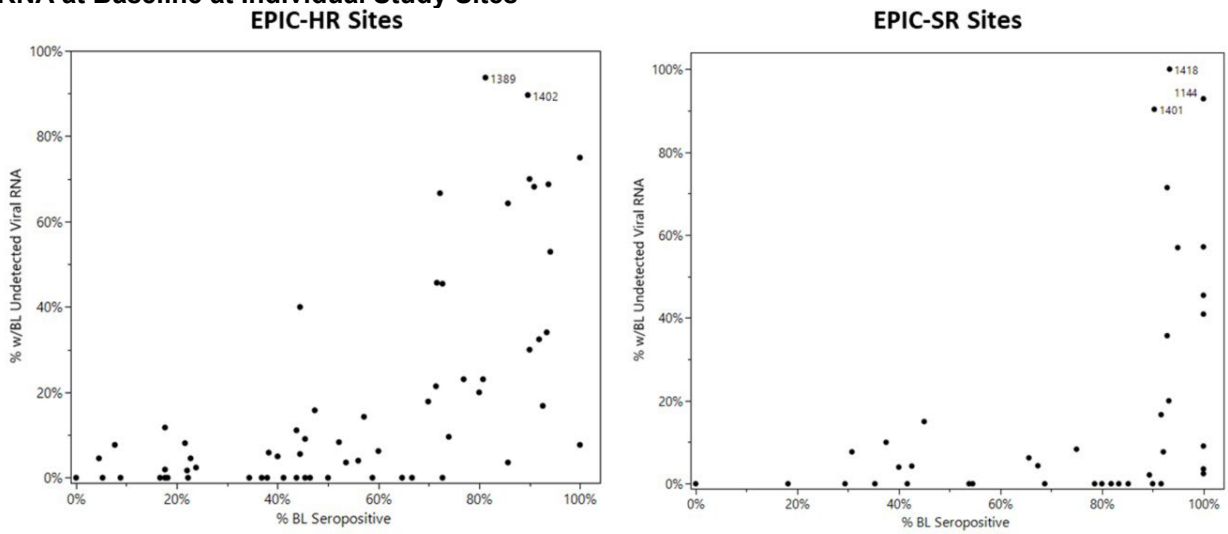


Source: FDA analysis of ADMC and ADSL datasets.
Note: Blue: PAXLOVID-treated subjects. Red: Placebo-treated subjects.
Note: Viral RNA results of detected/<LLOQ were assigned a value of 1.7 $\log_{10}$ copies/mL, and results of undetected RNA were assigned a value of 0 copies/mL.
Note: Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: CI, confidence interval; LLOQ, lower limit of quantitation; log, logarithm; RNA, ribonucleic acid; SITEID, site identifier

While an unusually high rate of undetected viral RNA results at a given site could indicate false or improper sampling from study volunteers, it might also be explained at least partly by the immunologic characteristics of the population, or even characteristics of the virus circulating at the time. Of note, the protocols allowed for up to 5 days from a positive RT-PCR test prior to randomization, so it is feasible for some study volunteers to test positive for SARS-CoV-2 infection but have undetected viral RNA by the time of randomization.

As expected, sites with larger percentages of subjects with undetected viral RNA at baseline also tended to have higher percentages of subjects with positive baseline serostatus (Figure 103). Nevertheless, even among sites with the highest seropositivity rates there was a wide range of percentages of subjects with undetected viral RNA at baseline. Two sites from EPIC-HR (1389 and 1402) and 3 sites from EPIC-SR (1144, 1401, 1418) are noted for having ≥90% of subjects with undetected viral RNA at baseline, and not surprisingly, for nearly all subjects with undetected viral RNA at baseline, viral RNA levels remained undetected at all subsequent study points.

Figure 103. Association Between Frequencies of SARS-CoV-2 Seropositivity and Undetected Viral RNA at Baseline at Individual Study Sites



Source: FDA analysis of ADMC and ADSL datasets.
Analysis includes sites with viral RNA data from ≥10 subjects.
Abbreviations: BL, baseline; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; w/, with

The noted sites with ≥90% of subjects with undetected viral RNA at baseline are all from the same Miami, FL, USA geographic area. EPIC-HR site 1389 is the same as EPIC-SR site 1401 (PI: Hernandez, Miami Lakes, FL, USA), and EPIC-HR site 1402 is the same as EPIC-SR site 1418 (PI: De La Vega, Hialeah Gardens, FL, USA). The third noted site (EPIC-SR site 1144) corresponds to EPIC-HR site 1147 (PI: Benitez, Hialeah, FL, USA), which had 68% of subjects in EPIC-HR with undetected viral RNA at baseline (91% seropositive). Interestingly, nearly all of the other sites with relatively low viral RNA levels across visits were also from the Miami, FL USA geographic area, including EPIC-HR sites 1318 (Miami, FL; same as 1388 in EPIC-SR), 1395 (Miami, FL), 1458 (Cutler Bay, FL), 1471 (Miami, FL), and 1505 (Miami, FL; same as 1520 in EPIC-SR). Notable exceptions in this same region are EPIC-HR 1274 and EPIC-SR 1281 (censored PI: Gonzalez/Martinez, Cutler Bay, FL) which had lower rates of baseline undetected viral RNA of 17% and 41%, respectively, despite high reported seropositivity rates of 93% and 100%, respectively. Another site that had low mean viral RNA levels across all visits was EPIC-HR 1362 (Bangalore, India), which is consistent with the Applicant's observations regarding some sites in India. Note that all EPIC-SR data from U.S. sites were from the 2021/Pre-Omicron period, which overlapped with the EPIC-HR enrollment period.

Given the close geographic clustering of sites with high frequencies of subjects with low or undetected viral RNA, it is reasonable to hypothesize a number of factors that could have caused or contributed to these observations, such as the immunologic status of the population, false positive screening test results, a virus lineage that tended to shed into the NP space at lower levels or for a shorter duration, the presence of genetic polymorphisms in the virus lineage that impacted the sensitivity of the qRT-PCR assay, or improper collection, handling or storage of samples. In response to an inquiry about these findings, the Applicant reported that sites with high frequencies of subjects with low or undetected viral RNA not only had high rates of SARS-CoV-2 seropositivity at baseline, but they also had higher quantitative levels of S-specific binding antibody. Therefore, the Applicant concluded that these observations reflect an expected inverse relationship between viral RNA level and the presence/level of anti-SARS-CoV-2

antibodies. No subjects at the sites with the highest frequencies of subjects with undetected viral RNA at baseline (EPIC-HR 1389, 1402; EPIC-SR 1144, 1401, 1418) reached the hospitalization/death endpoint. Furthermore, the inclusion of a subset of study subjects, irrespective of treatment arm, with undetected viral RNA at all study visits would not have a substantial impact on analyses of viral shedding or rebound. Therefore, no censoring or further investigations of these sites were considered.

18.5.4. Conclusions on Virology Data Anomalies and Approach to Censoring Data

The extensive analyses of viral RNA shedding patterns and viral nucleotide sequences summarized above indicate that virology data from sites EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez) and EPIC-SR site 1157 (Medzhidiev) are highly unusual and implausible, raising concerns about data quality or integrity from these sites. Given these concerning data patterns, the review team determined that these sites should be censored from all key efficacy, safety, and virology analyses.

The viral RNA and sequencing anomalies from EPIC-SR site 1197 (2022 enrollment period) were not as pronounced as those observed at the other noted sites. Nevertheless, the totality of data from this site indicate it is somewhat of an outlier in terms of similarities in viral RNA shedding patterns and viral RNA sequences between subjects within the site, as well as instances of identical or nearly identical viral sequences between this site and EPIC-SR site 1157. As a conservative approach, we recommended that data from EPIC-SR site 1197 (2022 enrollment period) similarly be censored from all key analyses, or at minimum for all virology-focused analyses.

Specific cause(s) of these virology data anomalies remain unknown. The fact that the anomalies appear to be restricted to three specific sites indicates a site-specific problem, such as mishandling of samples at the study sites prior to shipment to the central laboratory. However, it also seems somewhat improbable that similar problems occurred at three different study sites across two different countries over a ~one-year period, with two of the sites (both in Bulgaria) having subjects with identical or nearly identical viral nucleotide sequences.

The Applicant has concluded that central laboratory non-compliance, aliquoting, or run batch errors could not account for the viral RNA shedding patterns or viral sequencing concordance observed (discussed in (Pfizer 2022q)). The Applicant provided analyses of viral RNA results from EPIC-SR site 1157 (Medzhidiev), which were conducted across 17 different assay runs indicating that the viral RNA anomalies observed did not occur over a single assay run, and any sample mishandling that contributed to the patterns observed likely occurred upstream of the assay runs. Similarly, in the case of EPIC-HR site 1274/EPIC-SR site 1281 (Gonzalez/Martinez), samples were collected over a 5-month period (July-November 2021), and the Applicant concluded that the viral RNA shedding and sequencing data abnormalities could not be explained by concordance with batch run date of either qRT-PCR or viral sequencing since abnormalities were observed across multiple runs. Furthermore, the quality control data from viral sequencing runs did not indicate contamination or failed run issues. However, the Applicant did not provide data that excludes potential sample mishandling or mis-labeling at some early step in sample aliquoting or preparation (e.g., RNA extraction) that was batched by study site,

and occurred downstream of sample collection at the site but prior to any qRT-PCR or sequencing assay runs.

Sample mishandling directly at the study site could explain the results from site EPIC-HR 1274/EPIC-SR 1281 (Gonzalez/Martinez). This site had evidence of highly implausible symptom reporting data, (b) (7)(A) The intentional spiking or splitting of virology samples directly at the study site would be consistent with other findings at the site and could explain the virology data anomalies observed.

Importantly, regardless of the specific cause(s), there is no indication that any of the anomalies or potential mishandling of samples was in any manner related to specific treatment assignment. All conclusions on viral RNA shedding, rebound, and resistance remain unchanged regardless of how the data are censored from these study sites.

During the review another site that participated in both EPIC-HR and EPIC-SR, EPIC-HR 1470/EPIC-SR 1488 (PI: Hernandez), was closed during the conduct of the trials due to concerns about trial oversight, and existing subjects at the site were transferred to a nearby site (EPIC-HR 1276/EPIC-SR 1282; PI: Diaz). Issues at the original site were unrelated to any clinical virology data anomalies. The review team decided to censor all data from subjects who started at the EPIC-HR 1470/EPIC-SR 1488 site from all key analyses. See integrated review Section 6.3 for details.

In conclusion, the following sites/subjects were censored from all key clinical virology analyses of the EPIC-HR and EPIC-SR trials:

- EPIC-HR: Sites 1274 (Gonzalez/Martinez, n = 95 treated) and 1470 (including subjects [IDs that start with 1470] who transferred to 1276, n = 38 treated).
- EPIC-SR Pre-Omicron, data through December 19, 2021 cut-off: Sites 1281 (Gonzalez/Martinez, n = 46 treated), and 1488 (including subjects [IDs which start with 1488] who transferred to site 1282, n = 31 treated).
- EPIC-SR Post-Omicron, 2022 data: Sites 1157 (Medzhidiev, n = 47 treated) and 1197 (Haytova, 2022 enrollees only, n = 18 treated).
- Total number of subjects censored: 275 treated (133 in EPIC-HR, 142 in EPIC-SR; 137 PAXLOVID-treated, 138 placebo-treated).

19. Clinical Microbiology

Not applicable.

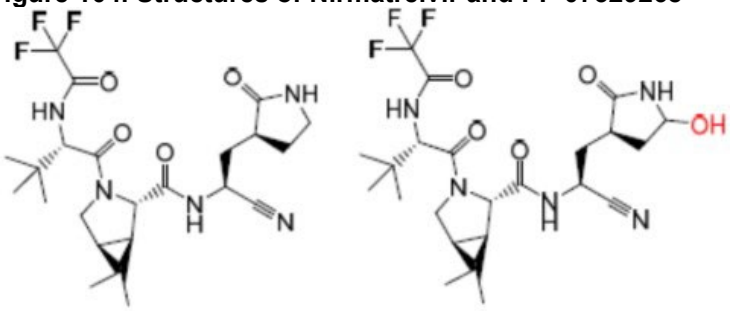
20. Mechanism of Action/Drug Resistance

20.1. Mechanism of Action

Inhibition of Recombinant SARS-CoV-2 M^{pro} in a Biochemical Assay (Pfizer 2022j)

The Applicant determined the ability of NIR and PF-07329268 (also referred to as M4) to inhibit recombinant SARS-CoV-2 (Wuhan-Hu-1) M^{pro} in a fluorescence resonance energy transfer (FRET)-based biochemical assay. PF-07329268 (Figure 104) is the primary oxidative metabolite of NIR in human and monkey liver microsomes, human and monkey hepatocytes, and monkey plasma. These experiments used 15 nM (~500 ng/mL) recombinant SARS-CoV-2 M^{pro}, 0.3 to 30,000 nM or 1 to 1,000 nM inhibitor, and 25,000 nM of a peptide substrate corresponding to the nsp4/nsp5 cleavage site (Dabcyl-KTSAVLQ↓SGFRKME-Edans). NIR inhibited the activity of recombinant SARS-CoV-2 M^{pro} with a geometric mean IC_{50} value of 19.2 nM and a geometric mean K_i value of 3.1 nM (Table 210). The metabolite PF-07329268 inhibited SARS-CoV-2 M^{pro} with a geometric mean IC_{50} value of 17.5 nM and a geometric mean K_i value of 3.2 nM.

Figure 104. Structures of Nirmatrelvir and PF-07329268



Source: Adapted from (Pfizer 2020a), p. 18.
Abbreviations: M4, metabolite 4 (PF-07329268); NIR, nirmatrelvir

Table 210. NIR and PF-07329268 Activity Against Recombinant SARS-CoV-2 M^{pro} in a Biochemical Assay

Compound	n	Geomean IC_{50} (nM)	CI (nM)	Geomean K_i (nM)	CI (nM)
NIR	6	19.2	13.5–25.0	3.1	1.3–4.9
PF-07329268	2	17.5	15.3–20.0[a]	3.2	2.4–4.2[a]

Source: (Pfizer 2022j), p. 9.
[a] The range is reported instead of CI since n=2.
Abbreviations: CI, 95% confidence interval; Geomean, geometric mean; IC_{50}, half-maximal inhibitory concentration; K_i, inhibition constant; M^{pro}, main protease; n, number of experiments; NIR, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Inhibition of Recombinant SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay (Pfizer 2022h)

Using the FRET-based biochemical assay, the Applicant determined the ability of NIR to inhibit recombinant SARS-CoV-2 M^{pro} containing 94 single substitutions and 21 combinations of

substitutions. These substitutions were tested because they: 1) represent naturally occurring or laboratory engineered substitutions at residues in direct contact or close proximity (<5 Å) with NIR, as determined by the Applicant's co-crystal structural analysis, 2) were identified as naturally occurring polymorphisms in M^{pro}, or 3) were associated with MHV or SARS-CoV-2 resistance to NIR in cell culture. These experiments were performed with 30 to 2,000 nM M^{pro} (depending on the catalytic efficiency of the enzyme), a maximum NIR concentration of 1,000 to 100,000 nM, and 30,000 nM of peptide substrate. In this set of experiments, NIR inhibited wild-type (WT, Wuhan-Hu-1) SARS-CoV-2 M^{pro} with a geometric mean K_i value of 0.9 nM (Table 211).

Results could not be obtained for M^{pro} H41Y, C145F/I, and H163A substitutions because the enzymes were catalytically inactive. These 3 residues directly contact NIR. Of the other single substitutions tested, 19/90 resulted in ≥3-fold higher geometric mean K_i values compared to WT: Y54A, F140A/L/S, G143S, S144A/E/T, H164N, E166A/G/V, H172Y, A173S/V, R188G, Q192L/P, and V297A (Table 211). Most of these residues directly contact or are located in close proximity (<5 Å) of NIR, except for A173S/V and V297A. The M^{pro} P132H substitution, which is a prevalent polymorphism in SARS-CoV-2 Omicron variants, did not affect NIR activity (K_i value fold-change: 0.7). In addition, 14/21 of the substitution combinations resulted in ≥3-fold higher geometric mean K_i values compared to WT. In most of these combinations, the primary M^{pro} substitution(s) responsible for the reduced activity of NIR appeared to be F140L, S144A, E166A/V, H172Y, and A173V.

Table 211. NIR Activity Against SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
WT	N/A	30	1,000	0.9	0.5	1.7	9	N/A	N/A
A7S	No	60	10,000	<0.8	<0.1	9.0	5	0.49	<0.9
A7T	No	70	10,000	<0.7	<0.1	8.8	5	0.46	<0.8
A7V	No	70	10,000	<0.8	<0.1	9.4	5	0.49	<0.9
G15S	No	55	1,000	1.4	0.5	4.3	4	0.11	1.6
T21I	No	40	1,000	1.4	0.2	9.6	3	0.17	1.6
T21I+L50F+ A193P+S301P	**No/No/No /No**	**150**	**10,000**	**6.5**	**2.1**	**19.8**	**3**	**0.0004**	**7.3**
T21I+S144A	**No/Yes**	**125**	**10,000**	**17.5**	**8.6**	**35.5**	**3**	**<0.0001**	**20**
T21I+S144A+T304I	**No/Yes/No**	**250**	**10,000**	**45.8**	**20.6**	**102**	**6**	**<0.0001**	**51**
T21I+E166V	**No/Yes**	**600**	**100,000**	**9,710**	**8,650**	**10,900**	**3**	**<0.0001**	**11,000**
T21I+A173V	**No/No**	**125**	**10,000**	**13.1**	**10.4**	**16.5**	**3**	**<0.0001**	**15**
T21I+A173V+T304I	**No/No/No**	**200**	**100,000**	**49.1**	**22.7**	**107**	**3**	**<0.0001**	**55**
T21I+A260V+T304I	No/No/No	200	10,000	<2.6	0.5	14.3	7	0.09	<2.9
T21I+T304I	No/No	60	10,000	<1.6	0.5	5.7	7	0.13	<1.8
L30F	No	150	10,000	<1.1	0.1	11.1	5	0.35	<1.3
H41Y[c]	Yes	--	--	--	--	--	--	--	--
T45I	No	30	1,000	1.8	1.1	3.1	4	0.01	2.1
M49I	Yes	45	1,000	0.2	<0.1	0.6	3	0.001	0.2
M49L	Yes	60	1,000	<0.5	0.2	1.2	4	0.10	<0.5
M49T	Yes	125	1,000/10,000	0.8	<0.1	32.2	3	0.39	0.9
L50F	No	60	1,000	0.2	<0.1	1.0	3	0.02	0.2
L50F+F140L+ L167F+T304I	**No/Yes/Yes/ No**	**300**	**100,000**	**169**	**114**	**252**	**3**	**<0.0001**	**190**
L50F+E166A+L167F	**No/Yes/Yes**	**300**	**10,000**	**187**	**109**	**321**	**3**	**<0.0001**	**210**
L50F+E166V	**No/Yes**	**500**	**100,000**	**4,020**	**2,250**	**7,170**	**3**	**<0.0001**	**4,500**
L50F+A173V	No/No	60	10,000	<1.7	0.2	12.2	4	0.16	<1.9
L50F+T304I	No/No	100	10,000	1.1	<0.1	25.0	4	0.37	1.3
Y54A	**Yes**	**500**	**10,000**	**22.0**	**14.2**	**34.3**	**4**	**<0.0001**	**25**
E55L	No	250	1,000/10,000	<0.6	0.3	1.3	7	0.26	<0.7
E55L+S144A	**No/Yes**	**250**	**10,000**	**49.8**	**23.8**	**104**	**3**	**<0.0001**	**56**
A70T	No	200	1,000/10,000	<0.3	0.2	0.5	5	0.007	<0.4
G71S	No	30	1,000	0.7	0.4	1.4	3	0.20	0.8

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
L75F	No	30	1,000	0.3	0.1	0.6	4	0.004	0.3
M82I	No	125	10,000	<1.7	0.1	20.9	5	0.23	<1.9
M82R	No	225	10,000	<0.8	0.1	4.4	5	0.50	<0.9
Q83K	No	30	1,000	0.9	0.3	2.5	4	0.37	1.0
K88R	No	30	1,000/10,000	0.4	0.2	1.0	4	0.13	0.5
L89F	No	60	1,000	1.8	0.5	7.1	4	0.08	2.1
K90R	No	30	1,000	1.1	0.2	5.8	5	0.35	1.2
K90R+K100R	No/No	60	1,000	<0.8	<0.1	6.3	3	0.48	<0.9
K90R+P252L	No/No	40	1,000	0.7	0.6	1.0	3	0.39	0.8
P108S	No	30	1,000	2.6	1.8	3.8	4	0.001	2.9
G109R	No	750	10,000	<0.8	<0.1	7.8	5	0.49	<0.9
P132H	No	60	1,000	0.6	0.2	2.3	4	0.08	0.7
P132L	No	60	1,000	1.0	0.2	4.6	3	0.32	1.1
P132S	No	100	1,000	0.6	<0.1	4.1	4	0.19	0.6
P132H+T169S	No/No	60	1,000	1.0	0.3	3.9	4	0.33	1.1
T135I	No	45	1,000	2.0	0.9	4.5	4	0.02	2.3
T135I+T304I	**No/No**	**100**	**10,000**	**<4.6**	**0.7**	**31.6**	**7**	**0.04**	**<5.1**
F140A	**Yes**	**250**	**10,000**	**18.3**	**3.4**	**99.3**	**7**	**0.002**	**21**
F140L	**Yes**	**40**	**1,000**	**6.8**	**2.0**	**22.8**	**5**	**0.002**	**7.6**
F140L+A173V	**Yes/No**	**125**	**10,000**	**85.0**	**69.8**	**103**	**3**	**<0.0001**	**95**
F140S	**Yes**	**400**	**10,000**	**227**	**86.3**	**599**	**4**	**<0.0001**	**260**
L141F	Yes	50	10,000	1.7	0.4	7.4	3	0.07	1.9
N142L	Yes	35	1,000	1.0	0.3	4.0	5	0.33	1.2
N142S	Yes	30	1,000	<0.7	0.3	1.8	6	0.36	<0.8
G143S	**Yes**	**300**	**1,000/10,000**	**3.2**	**0.2**	**46.9**	**5**	**0.21**	**3.6**
S144A	**Yes**	**250**	**10,000**	**41.3**	**18.7**	**91.2**	**3**	**<0.0001**	**46**
S144E	**Yes**	**1,250**	**10,000**	**427**	**238**	**769**	**4**	**<0.0001**	**480**
S144T	**Yes**	**1,250**	**10,000**	**151**	**49.8**	**461**	**3**	**<0.0001**	**170**
C145F[c]	Yes	--	--	--	--	--	--	--	--
C145I[c]	Yes	--	--	--	--	--	--	--	--
D153H	No	60	10,000	1.1	<0.1	61.8	3	0.40	1.3
D153Y	No	60	10,000	1.1	0.1	8.7	4	0.45	1.3
V157A	No	125	10,000	<1.0	0.2	4.2	4	0.36	<1.1
S158P	No	300	10,000	1.1	0.3	4.3	4	0.27	1.3
C160F	No	60	10,000	0.5	<0.1	9.8	3	0.31	0.6

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
H163A[c]	Yes	--	--	--	--	--	--	--	--
H164N	**Yes**	**250**	**10,000**	**<6.0**	**2.0**	**18.3**	**8**	**0.002**	**<6.7**
M165I	Yes	60	1,000	<0.7	<0.1	5.4	4	0.41	<0.8
E166A	**Yes**	**250**	**10,000**	**31.2**	**15.1**	**64.3**	**6**	**<0.0001**	**35**
E166G	**Yes**	**500**	**10,000**	**<5.6**	**0.2**	**130**	**4**	**0.07**	**<6.2**
E166V	**Yes**	**2,000**	**100,000**	**6,880**	**5,670**	**8,360**	**3**	**<0.0001**	**7,700**
L167F	Yes	250	10,000	<0.8	<0.1	61.7	3	0.49	<0.9
L167I	Yes	60	1,000	1.6	0.5	5.3	3	0.06	1.8
P168R	Yes	60	1,000	1.7	0.7	4.1	4	0.06	1.9
P168S	Yes	30	1,000	0.5	<0.1	3.1	4	0.25	0.6
T169I	No	60	10,000	<1.2	<0.1	25.1	3	0.31	<1.4
H172Y	**Yes**	**500**	**1,000/10,000**	**225**	**130**	**391**	**4**	**<0.0001**	**250**
H172Y+P252L	**Yes/No**	**750**	**100,000**	**161**	**33.3**	**782**	**3**	**<0.0001**	**180**
A173S	**No**	**30**	**10,000**	**3.7**	**1.2**	**11.3**	**4**	**0.006**	**4.1**
A173T	No	70	10,000	<1.6	<0.1	84.8	4	0.30	<1.8
A173V	**No**	**200**	**10,000**	**14.3**	**2.4**	**83.6**	**4**	**0.003**	**16**
A173V+T304I	**No/No**	**250**	**10,000**	**24.5**	**5.5**	**109**	**6**	**0.0004**	**28**
V186A	Yes	100	10,000	<0.8	0.1	5.6	3	0.46	<0.8
V186G	Yes	500	10,000	<1.2	<0.1	28.4	4	0.36	<1.4
R188G	**Yes**	**250**	**100,000**	**33.7**	**18.3**	**62.0**	**3**	**<0.0001**	**38**
R188M	Yes	60	1,000	0.9	0.4	2.3	4	0.37	1.0
Q189K	Yes	500	1,000/10,000	<1.5	0.3	6.5	6	0.18	<1.6
T190A	Yes	60	1,000	0.5	<0.1	8.3	3	0.17	0.6
T190I	Yes	30	1,000	0.6	0.2	1.8	3	0.23	0.7
A191T	Yes	30	1,000	<0.7	0.3	2.0	4	0.40	<0.8
A191V	Yes	30	1,000	<0.7	0.4	1.4	5	0.37	<0.8
Q192L	**Yes**	**625**	**10,000**	**26.3**	**14.7**	**46.8**	**3**	**<0.0001**	**29**
Q192P	**Yes**	**1,000**	**10,000**	**<6.9**	**0.2**	**213**	**4**	**0.15**	**<7.8**
A193P	No	125	10,000	0.8	<0.1	26.1	3	0.49	0.9
T196A	No	60	10,000	1.1	0.1	10.2	4	0.25	1.2
T196K	No	60	10,000	<0.3	ND	ND	5	0.003	<0.3
T196M	No	60	10,000	0.7	<0.1	20.5	4	0.13	0.8
T196R	No	60	10,000	<0.5	0.3	0.9	9	0.15	<0.6
V212F	No	30	1,000	0.4	0.2	0.8	6	0.06	0.5
I213L	No	60	1,000	0.4	<0.1	12.9	3	0.09	0.5

M^{pro} Enzyme	Contact?[a]	Enzyme (nM)	Max NIR (nM)	K_i Geomean (nM)	K_i Lower 95% CI (nM)	K_i Upper 95% CI (nM)	n	p-Value (vs. WT)[b]	K_i Fold Change (vs. WT)
L220F	No	30	1,000	<0.8	0.3	2.0	5	0.47	<0.9
A234V	No	30	1,000	1.4	0.6	3.0	5	0.09	1.6
D248E	No	30	1,000	1.3	0.2	7.7	4	0.25	1.4
P252L	No	30	1,000/10,000	<0.8	0.3	1.9	6	0.43	<0.9
L253V	No	60	1,000	<0.6	0.3	1.3	7	0.34	<0.7
A260V	No	40	1,000	0.5	0.1	2.1	4	0.12	0.6
A266V	No	60	1,000	1.3	0.3	4.7	5	0.21	1.4
G278R	No	60	10,000	<0.7	0.3	1.8	5	0.36	<0.8
G278V	No	60	10,000	2.1	0.3	15.1	3	0.08	2.4
V296I	No	125	10,000	<0.7	0.2	1.9	6	0.35	<0.7
V297A	**No**	**60**	**10,000**	**2.6**	**0.2**	**44.0**	**5**	**0.15**	**3.0**
V297F	No	60	10,000	<2.5	<0.1	94.9	4	0.13	<2.8
S301P	No	125	10,000	0.2	ND	ND	1	0.003	0.2
G302C	No	125	10,000	1.6	0.3	7.2	4	0.13	1.8
T304I	No	80	1,000	0.9	0.4	2.0	4	0.42	1.0

Source: Adapted from (Pfizer 2022h), p. 16-17.
Note: Bolded rows indicates substitutions that resulted in ≥3-to-<10-fold increases in geomean K_i values. Bolded and shaded rows indicate substitutions that resulted in ≥10-fold increases in geomean K_i values.
[a.] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[b.] p-values were determined by t-test of log Ki values with one tail and unequal variance.
[c.] No data (inactive enzyme).
Abbreviations: CI, confidence interval; K_i, inhibition constant; M^{pro}, main protease; n, number of experiments; N/A, not applicable; WT, wild-type.

The Applicant also determined the catalytic efficiency (k_{cat}/K_m) of these M^{pro} enzymes in the absence of NIR. These experiments were performed with variable concentrations of M^{pro} and a maximum peptide substrate concentration of 250,000 nM. WT SARS-CoV-2 M^{pro} had a catalytic efficiency (k_{cat}/K_m) of 25,500 $M^{-1}s^{-1}$ (Table 212). Of the 33 M^{pro} enzymes with ≥3-fold higher geometric mean K_i values, 31/33 (all except A173S and V297A) had ≥3-fold lower geometric mean k_{cat}/K_m values, indicating reduced catalytic efficiency. These results indicate that most M^{pro} substitutions that lead to reduced NIR activity also result in reduced catalytic efficiency of the enzyme. However, the extent to which these results are predictive of virus replication kinetics in cell culture or in SARS-CoV-2-infected individuals is unclear. Furthermore, these findings do not take into account the possibility that SARS-CoV-2 could acquire additional compensatory substitutions that further improve the catalytic activity of NIR-resistant M^{pro} enzymes.

Table 212. Catalytic Efficiency of SARS-CoV-2 M^{pro} Enzymes With Substitutions in a Biochemical Assay

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
WT	N/A	25,500	18,300	35,600	15	N/A	N/A
A7S	No	12,800	5,140	31,900	4	0.04	2.0
A7T	No	7,150	6,080	8,400	3	<0.0001	3.6
A7V	No	6,350	3,830	10,500	3	<0.0001	4.0
G15S	No	21,300	12,000	37,700	6	0.26	1.2
T21I	No	16,800	13,400	21,100	3	0.01	1.5
T21I+L50F+ A193P+S301P	**No/No/No/No**	**7,800**	**4,060**	**15,000**	**3**	**0.0004**	**3.3**
T21I+S144A	**No/Yes**	**6,640**	**3,900**	**11,300**	**3**	**<0.0001**	**3.8**
T21I+S144A+T304I	**No/Yes/No**	**2,760**	**1,150**	**6,600**	**3**	**0.0002**	**9.2**
T21I+E166V	**No/Yes**	**1,270**	**883**	**1,820**	**3**	**<0.0001**	**20**
T21I+A173V	**No/No**	**7,200**	**4,170**	**12,400**	**3**	**<0.0001**	**3.5**
T21I+A173V+T304I	**No/No/No**	**5,920**	**3,640**	**9,640**	**3**	**<0.0001**	**4.3**
T21I+A260V+T304I	No/No/No	4,470	2,560	7,820	3	<0.0001	5.7
T21I+T304I	No/No	14,900	10,800	20,600	3	0.004	1.7
L30F	No	2,490	316	19,700	3	0.01	10
T45I	No	29,800	18,500	48,000	8	0.27	0.9
M49I	Yes	15,500	7,170	33,600	4	0.16	1.6
M49L	Yes	14,900	10,200	21,900	6	0.01	1.7
M49T	Yes	6,700	4,790	9,380	5	<0.0001	3.8
L50F	No	12,000	5,170	27,900	5	0.007	2.1
L50F+F140L+ L167F+T304I	**No/Yes/Yes/No**	**2,780**	**1,430**	**5,410**	**3**	**<0.0001**	**9.2**
L50F+E166A+L167F	**No/Yes/Yes**	**1,110**	**917**	**1,340**	**3**	**<0.0001**	**23**
L50F+E166V	**No/Yes**	**703**	**346**	**1,430**	**4**	**<0.0001**	**36**
L50F+A173V	No/No	10,100	2,780	36,900	3	2.5	0.03
L50F+T304I	No/No	8,340	6,590	10,600	3	<0.0001	3.1
Y54A	**Yes**	**507**	**150**	**1,710**	**4**	**0.0003**	**50**
E55L	No	8,680	3,840	19,600	5	0.008	2.9
E55L+S144A	**No/Yes**	**3,720**	**850**	**16,200**	**4**	**0.01**	**6.9**
A70T	No	11,700	3,270	41,600	4	0.07	2.2
G71S	No	15,700	6,150	40,300	3	0.07	1.6
L75F	No	33,400	13,900	80,400	3	0.17	0.8

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
M82I	No	5,320	2,550	11,100	3	0.0002	4.8
M82R	No	4,560	1,730	12,000	3	0.001	5.6
Q83K	No	32,900	17,000	63,600	4	0.18	0.8
K88R	No	28,300	12,100	65,700	4	0.38	0.9
L89F	No	15,900	10,500	24,200	9	0.03	1.6
K90R	No	28,400	16,000	50,400	9	0.36	0.9
K90R+K100R	No/No	9,620	2,310	40,000	3	0.12	2.7
K90R+P252L	No/No	11,900	2,820	50,200	3	0.07	2.1
P108S	No	27,100	18,000	40,800	10	0.41	0.9
G109R	No	722	246	2,120	5	0.0001	35
P132H	No	17,800	3,690	85,800	3	0.22	1.4
P132L	No	12,700	4,230	38,200	3	0.04	2.0
P132S	No	4,790	716	32,100	3	0.02	5.3
P132H+T169S	No/No	11,800	8,310	16,900	5	0.0009	2.2
T135I	No	17,000	10,100	28,600	5	0.06	1.5
T135I+T304I	**No/No**	**6,350**	**3,130**	**12,900**	**3**	**0.0003**	**4.0**
F140A	**Yes**	**2,060**	**102**	**41,800**	**3**	**0.03**	**12**
F140L	**Yes**	**6,890**	**1,790**	**26,500**	**3**	**0.02**	**3.7**
F140L+A173V	**Yes/No**	**3,120**	**2,660**	**3,670**	**3**	**<0.0001**	**8.2**
F140S	**Yes**	**833**	**574**	**1,210**	**3**	**<0.0001**	**31**
L141F	Yes	20,000	10,200	39,100	3	0.15	1.3
N142L	Yes	48,000	27,900	82,700	5	0.02	1.4
N142S	Yes	18,300	9,340	35,900	5	0.14	1.9
G143S	**Yes**	**1,310**	**537**	**3,210**	**5**	**0.0001**	**19**
S144A	**Yes**	**6,570**	**2,390**	**18,000**	**3**	**0.004**	**3.9**
S144E	**Yes**	**69.0**	**49.3**	**96.5**	**4**	**<0.0001**	**370**
S144T	**Yes**	**88.7**	**47.9**	**164**	**4**	**<0.0001**	**290**
D153H	No	15,300	3,970	58,900	4	0.16	1.7
D153Y	No	12,500	3,800	40,900	4	0.07	2.0
V157A	No	8,660	5,950	12,600	6	0.0001	2.9
S158P	No	2,790	2,110	3,700	6	<0.0001	9.1
C160F	No	14,100	4,760	41,700	3	0.06	1.8
H164N	**Yes**	**1,350**	**229**	**7,980**	**3**	**0.005**	**19**
M165I	Yes	15,300	7,130	33,000	6	0.08	1.7
E166A	**Yes**	**2,420**	**645**	**9,080**	**3**	**0.003**	**11**
E166G	**Yes**	**1,440**	**847**	**2,450**	**4**	**<0.0001**	**18**
E166V	**Yes**	**283**	**224**	**357**	**5**	**<0.0001**	**90**
L167F	Yes	2,200	391	12,300	3	0.007	12
L167I	Yes	14,200	7,970	25,200	8	0.03	1.8
P168R	Yes	15,900	11,500	22,000	5	0.01	1.6
P168S	Yes	40,900	29,200	57,200	5	0.02	0.6
T169I	No	14,500	4,950	42,400	3	0.07	1.8
H172Y	**Yes**	**427**	**173**	**1,050**	**5**	**<0.0001**	**60**
H172Y+P252L	**Yes/No**	**950**	**712**	**1,270**	**3**	**<0.0001**	**27**
A173S	**No**	**12,200**	**6,130**	**24,100**	**3**	**0.007**	**2.1**
A173T	No	4,280	1,860	9,880	3	0.0004	6.0
A173V	**No**	**4,460**	**2,910**	**6,830**	**6**	**<0.0001**	**5.7**
A173V+T304I	**No/No**	**2,740**	**1,290**	**5,810**	**3**	**<0.0001**	**9.3**
V186A	Yes	8,410	4,840	14,600	3	0.0002	3.0

M^{pro}	Contact?[a]	k_{cat}/K_m Geomean ($M^{-1}s^{-1}$)	k_{cat}/K_m Lower 95% CI ($M^{-1}s^{-1}$)	k_{cat}/K_m Upper 95% CI ($M^{-1}s^{-1}$)	n	p-Value (vs. WT)[b]	k_{cat}/K_m Fold Change (vs. WT)
V186G	Yes	1,540	1,120	2,120	5	<0.0001	17
R188G	**Yes**	**4,870**	**2,270**	**10,400**	**3**	**0.0002**	**5.2**
R188M	Yes	11,500	8,500	15,400	6	0.0003	2.2
Q189K	Yes	2,330	1,740	3,120	7	<0.0001	11
T190A	Yes	6,150	5,160	7,340	5	<0.0001	4.1
T190I	Yes	22,100	15,300	31,900	5	0.25	1.2
A191T	Yes	23,300	15,100	36,000	6	0.35	1.1
A191V	Yes	43,100	18,500	100,000	6	0.09	0.6
Q192L	**Yes**	**292**	**126**	**679**	**4**	**<0.0001**	**87**
Q192P	**Yes**	**539**	**282**	**1,030**	**4**	**<0.0001**	**47**
A193P	No	7,160	3,780	13,500	3	0.0002	3.6
T196A	No	10,100	4,170	24,300	4	0.02	2.5
T196K	No	14,500	11,400	18,500	3	0.001	1.8
T196M	No	13,000	5,980	28,100	3	0.02	2.0
T196R	No	14,200	5,880	34,400	4	0.06	1.8
V212F	No	26,700	13,000	54,800	5	0.44	1.0
I213L	No	16,100	7,160	36,200	3	0.06	1.6
L220F	No	23,800	9,530	59,400	3	0.40	1.1
A234V	No	24,100	14,300	40,500	8	0.42	1.1
D248E	No	20,500	8,200	51,500	5	0.29	1.2
P252L	No	30,800	11,500	83,000	4	0.31	0.8
L253V	No	10,400	4,780	22,700	5	0.01	2.5
A260V	No	10,100	3,290	30,800	3	0.02	2.5
A266V	No	20,700	3,440	125,000	3	0.34	1.2
G278R	No	16,200	8,420	31,200	3	0.04	1.6
G278V	No	16,100	6,430	40,100	3	0.07	1.6
V296I	No	12,100	2,350	62,300	3	0.09	2.1
V297A	**No**	**10,700**	**7,040**	**16,200**	**4**	**0.0005**	**2.4**
V297F	No	11,100	7,260	17,000	4	0.0008	2.3
S301P	No	7,210	3,820	13,600	3	0.0002	3.5
G302C	No	7,770	5,340	11,300	6	<0.0001	3.3
T304I	No	9,200	6,390	13,200	6	0.0001	2.8

Source: Adapted from (Pfizer 2022h), p. 18-19.
Note: Bolded rows indicates substitutions that resulted in ≥3-to-<10-fold increases in geomean K_i values. Bolded and shaded rows text indicate substitutions that resulted in ≥10-fold increases in geomean K_i values..
[a] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[b] p-values were determined by t-test (details not provided).
Abbreviations: CI, confidence interval; k_{cat}, first-order rate constant; K_i, inhibition constant; K_m, Michaelis constant (substrate concentration at half the maximum velocity); M^{pro}, main protease; n, number of experiments; N/A, not applicable; WT, wild-type

Inhibition of Recombinant M^{pro} Enzymes from Six Other Human CoVs in Biochemical Assays (Pfizer 2021d)

Using FRET-based biochemical assays, the Applicant determined the ability of NIR to inhibit recombinant M^{pro} enzymes from 6 other human coronaviruses: SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-HKU1 are betacoronaviruses, like SARS-CoV-2, whereas HCoV-NL63 and HCoV-229E are alphacoronaviruses. These experiments were performed with 12.5 to 100 nM recombinant M^{pro}, a maximum NIR concentration of 30,000 nM, and

12,500 to 25,000 nM of peptide substrates. For SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-HKU1 (betacoronaviruses), the SARS-CoV-2 nsp4/nsp5 peptide substrate was used, but for HCoV-NL63 and HCoV-229E (alphacoronaviruses), their respective nsp4/nsp5 peptide substrates were used. NIR inhibited the activity of all 6 M^{pro} enzymes tested, with geometric mean IC_{50} values of 28.9 to 479 nM (Table 213). However, relative to SARS-CoV-2 M^{pro} (geometric mean IC_{50} value: 19.2 nM), there was a ≥10-fold increase in geometric mean IC_{50} values for MERS-CoV and HCoV-NL63 M^{pro} enzymes, indicating reduced NIR activity.

Table 213. NIR Activity Against Other Human CoV M^{pro} Enzymes in Biochemical Assays

M^{pro}	n	Enzyme (nM)	Substrate (nM)	Geomean IC_{50} (nM)	95% CI
SARS-CoV-1	3	25	25,000	28.9	24.4-34.2
MERS-CoV	3	100	25,000	402	218-741
HCoV-OC43	3	25	12,500	77.7	31.2-194
HCoV-HKU1	3	12.5	12,500	39.1	25.6-59.8
HCoV-NL63	3	50	12,500	479	242-949
HCoV-229E	3	50	12,500	113	41.7-304

Source: Adapted from (Pfizer 2021d), p. 9, 13.
Abbreviations: CI, confidence interval; CoV, coronavirus; Geomean, geometric mean; IC_{50}, half-maximal inhibitory concentration; M^{pro}, main protease; n, number of experiments; NIR, nirmatrelvir.

Inhibition of Other Proteases in Biochemical Assays (Pfizer 2021d)

Using FRET-based biochemical assays, the Applicant determined the ability of NIR to inhibit 7 human proteases (caspase 2, cathepsins B/D/L, elastase, thrombin a, and chymotrypsin), 1 bovine protease (chymotrypsin), and 1 viral protease (HIV-1). These proteases are unrelated to SARS-CoV-2 M^{pro}. Caspase 2 and cathepsins B/L are cysteine proteases, like SARS-CoV-2 M^{pro}, whereas the others are aspartic or serine proteases (Table 214). Cathepsins B/L have been implicated in SARS-CoV-2 entry (Zhao et al. 2021), and dual inhibitors of SARS-CoV-2 M^{pro} and cathepsins B/L have been identified (Sacco et al. 2020). These experiments were performed with 0.01 to 20 nM enzyme, a maximum NIR concentration of 10,000 or 100,000 nM, and 2,000 to 750,000 nM of peptide substrate. NIR did not inhibit any of the proteases tested up to 10,000 or 100,000 nM (Table 214). These findings indicate that the activity of NIR may be restricted to M^{pro} enzymes.

Table 214. NIR Activity Against Other Proteases in Biochemical Assays

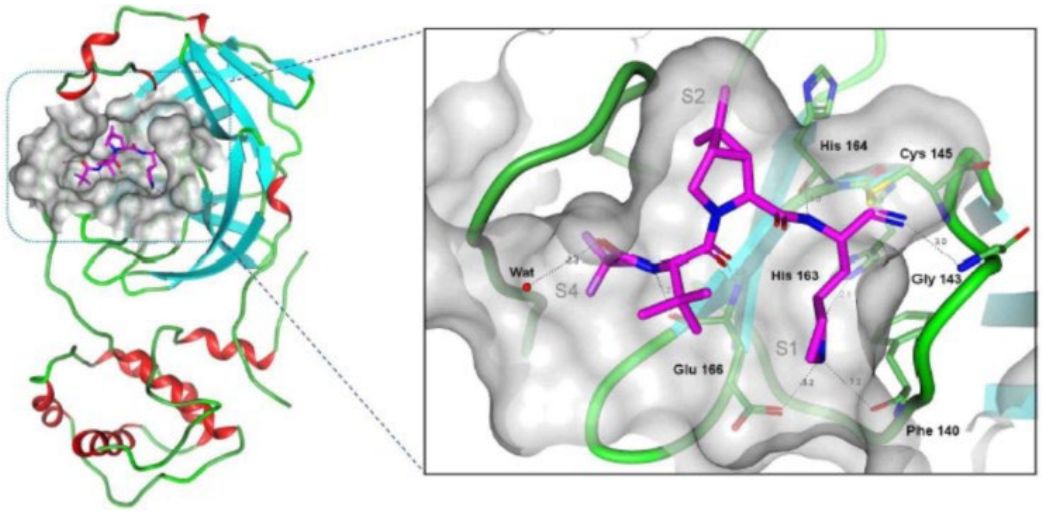
Protease	n	Type	Enzyme (nM)	Substrate (nM)	IC_{50} (nM)
Caspase 2	2	Cysteine	10	5,000	>100,000
Cathepsin B	3	Cysteine	1.2	15,000	>100,000
Cathepsin D	2	Aspartic	1	2,000	>100,000
Cathepsin L	3	Cysteine	0.25	10,000	>100,000
Elastase	2	Serine	0.6	10,000	>100,000
Thrombin a	2	Serine	0.01	10,000	>100,000
Chymotrypsin	2	Serine	2	750,000	>10,000
Bovine chymotrypsin	2	Serine	0.5	10,000	>100,000
HIV-1	2	Aspartic	20	10,000	>100,000

Source: Adapted from (Pfizer 2021d), p. 10, 13.
Abbreviations: HIV-1, human immunodeficiency virus type-1; IC_{50}, half-maximal inhibitory concentration; n, number of experiments; NIR, nirmatrelvir

X-Ray Co-Crystal Structure of NIR Bound to Recombinant SARS-CoV-2 M^{pro} (Pfizer 2022s)

Using X-ray crystallography, the Applicant determined the co-crystal structure of NIR bound to recombinant SARS-CoV-2 M^{pro} (Wuhan-Hu-1, with an additional glycine residue on the N-terminus) at 1.7 Å resolution. NIR was found to bind to the active site of SARS-CoV-2 M^{pro}, forming interactions that are analogous to enzyme-substrate contacts (Figure 105). The warhead nitrile carbon of NIR covalently binds to the sulfur atom from C145, generating a thioimidate complex, while the imine nitrogen hydrogen bonds with the main chain NH of G143. The lactam of NIR binds to the S1 pocket of M^{pro} and hydrogen bonds with the side chains of H163 and E166, as well as the main chain CO of F140. In addition, the central amide NH of NIR hydrogen bonds to the CO of H164. The dimethyl aza-bicyclohexane moiety of NIR binds to the hydrophobic S2 pocket, while the trifluoroacetamide moiety of NIR binds to the S4 pocket. The dimethylpropyl moiety of NIR is exposed to solvent.

Figure 105. Co-Crystal Structural Analysis of NIR Bound to SARS-CoV-2 M^{pro}



Source: (Pfizer 2022s), p. 8.
Note: NIR binds to the substrate site of SARS-CoV-2 M^{pro} and forms a covalent bond with the catalytic cysteine residue, C145. Furthermore, NIR occupies the S1, S2, and S4 binding pockets of the active site. Residues that form hydrogen bonds (dashed lines) with NIR are labeled.
Abbreviations: Cys, cysteine; Glu, glutamic acid; Gly, glycine; His, histidine; M^{pro}, main protease; NIR, nirmatrelvir; Phe, phenylalanine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Sequence Conservation of NIR Contact Residues in SARS-CoV-2 M^{pro} (Pfizer 2022r)

Based on co-crystal structural analysis, the Applicant identified 23 SARS-CoV-2 M^{pro} residues that directly contact or are located in close proximity (<5 Å) of NIR (Table 215). Of these, 11/23 residues directly contact NIR, while 12/23 are located in close proximity but do not directly contact NIR. The Applicant assessed the conservation of these residues in SARS-CoV-2 using the EpiCoV sequence database hosted by GISAID (accessed November 30, 2022; n = 12,664,696 sequences). Note that sequence databases are affected by differences in the amount of sequencing conducted across countries and geographical regions. All 23 residues were highly conserved, with polymorphism frequencies ≤0.1%. The most common polymorphisms were M49I (n = 1,950), V186F (n = 2,193), T190I (n = 2,032), and A191V (n = 9,140). M49I, T190I,

and A191V did not affect NIR activity in a biochemical assay, while V186F was not tested, although V186A/G did not affect NIR activity in a biochemical assay. Several of these naturally occurring M^{pro} polymorphisms were associated with NIR resistance in cell culture (typically in combination with other M^{pro} substitutions) in studies conducted by the Applicant or others, including F140L (n = 4), S144A (n = 12), E166A/V (n = 9 each), L167F (n = 5), H172Y (n = 12), V186A (n = 47), R188G (n = 15), and A191V (n = 9,140) (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023).

Table 215. Sequence Conservation of SARS-CoV-2 M^{pro} Residues That Contact or Are Located in Close Proximity (<5 Å) of NIR

M^{pro} Residue	# Sequences With Polymorphisms	Percentage of Sequences With Polymorphisms	Polymorphisms in ≥100 Sequences	Distance From NIR (Å)	Interaction With NIR
H41	199	0.002%	H41Q	3.5	Catalytic residue, hydrophobic contact
M49	2,127	0.02%	M49I	3.8	Side chain hydrophobic contact
Y54	15	0.0001%	none	3.7	No direct interaction
F140	22	0.0002%	none	3.2	Backbone hydrogen bond
L141	52	0.0004%	none	3.9	No direct interaction
N142	278	0.002%	N142S	3.8	No direct interaction
G143	26	0.0002%	none	3.0	Backbone hydrogen bond
S144	42	0.0003%	none	3.6	No direct interaction
C145	24	0.0002%	none	1.9	Catalytic residue, covalent bond
H163	15	0.0001%	none	2.8	Side chain hydrogen bond
H164	14	0.0001%	none	3.0	Backbone hydrogen bond
M165	139	0.001%	M165I	2.8	Side chain hydrophobic contact
E166	52	0.0004%	none	3.6	Backbone and side chain hydrogen bonds
L167	16	0.0001%	none	3.5	Side chain hydrophobic contact
P168	497	0.004%	P168S	3.3	Side chain hydrophobic contact
H172	56	0.0004%	none	3.5	No direct interaction
V186	3,551	0.03%	V186F/G/I	4.6	No direct interaction
D187	113	0.0009%	none	3.7	No direct interaction
R188	561	0.004%	R188K/S	3.7	No direct interaction
Q189	146	0.001%	none	3.8	No direct interaction
T190	2,156	0.02%	T190I	2.8	No direct interaction
A191	10,178	0.08%	A191S/T/V	4.7	No direct interaction
Q192	111	0.0009%	none	3.5	No direct interaction

Source: Adapted from (Pfizer 2022r), p. 10-16.
Yellow text and red text indicate Mpro residues at which substitutions resulted in ≥3-to-<10-fold and ≥10-fold increases in geomean Ki values, respectively, in a biochemical assay.
Abbreviations: Mpro, main protease; NIR, nirmatrelvir

Other Studies Related to NIR Mechanism of Action

- In the Duveau study, the ability of NIR to inhibit SARS-CoV-2 M^{pro}, SARS-CoV-2 papain-like protease, and 21 human cysteine proteases was determined using biochemical assays. The activity of NIR was selective for SARS-CoV-2 M^{pro} (Duveau and Thomas 2022).
- In Greasley et al., the Applicant solved the co-crystal structure of NIR bound to SARS-CoV-2 Omicron M^{pro} (P132H) and determined that there were no significant differences in the structure relative to WT M^{pro} (Greasley et al. 2022).
- In Kneller et al., Yang et al., and Zhao et al., the co-crystal structure of NIR bound to SARS-CoV-2 M^{pro} was independently determined (Kneller et al. 2022; Yang et al. 2022; Zhao et al.

2022). In (Yang et al. 2022), the 3 structures were compared to each other and 2 structures published by the Applicant (Owen et al. 2021). All 5 structures were highly similar, but several M^{pro} residues had variable orientations, including 3 residues that contact NIR or have been associated with NIR resistance in cell culture (M49, L50, P168).

20.2. Nonclinical Virology

20.2.1. Antiviral Activity in Cell Culture

NIR Activity Against SARS-CoV-2 WA1/2020 in Vero E6 Cells (Pfizer 2021h)

The activity of NIR and PF-07329268 (the primary oxidative metabolite of NIR) against SARS-CoV-2 USA-WA1/2020 was investigated in Vero E6 (African green monkey kidney) cells by cytopathic effect (CPE) reduction assay. Vero E6 cells were infected at a multiplicity of infection (MOI) of ~0.002, and compounds were added at the time of infection. CPE reduction was measured 3 days post-infection using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). Cell viability was measured in uninfected cells treated with NIR in parallel under matched conditions. These experiments were performed in the presence and absence of 2,000 nM CP-100356, a P-gp inhibitor. According to the Applicant, NIR is a P-gp substrate, and Vero E6 cells express high levels of P-gp, such that NIR has enhanced activity in Vero E6 cells treated with CP-100356. In the absence of CP-100356, NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 4,480 and 9,460 nM, respectively (Table 216). In the presence of CP-100356, NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 74.5 and 155 nM, respectively. Thus, NIR had 60-61-fold more potent activity in the presence of CP-100356. In uninfected cells, NIR did not affect cell viability up to the maximum concentration tested (10,000 or 100,000 nM), resulting in average selectivity index (SI) values of >21.5 and >1,250 in the absence and presence of CP-100356, respectively. PF-07329268 also had more potent activity in the presence of CP-100356, but PF-07329268 had ~9.3-fold weaker activity than NIR in the presence of CP-100356.

Table 216. Activity of NIR and PF-07329268 (±CP-100356) Against SARS-CoV-2 in Vero E6 Cells

NIR				NIR + CP-100356			
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI
4,480, n = 20 (3,550-5,650)	9,460, n = 20 (7,600-11,800)	>100,000 or >10,000, n = 10	>21.5	74.5, n = 20 (66.5-83.4)	155, n = 20 (138-173)	>100,000 or >10,000, n = 10	>1,250

PF-07329268				PF-07329268 + CP-100356			
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI
>3,333 or >3,000, n = 4 (ND)	>3,333 or >3,000, n = 4 (ND)	>3,333 or >3,000, n = 2	ND	690, n = 3 (210 – 2,270)	1,440, n = 3 (437 – 4,720)	>3,333 or >3,000, n = 2	>5.1

Source: Adapted from (Pfizer 2021h), p. 12.
Note: CP-100356 is a P-gp inh bitor that was added to a final concentration of 2,000 nM.
Abbreviations: CC_{50}, 50% cytotoxic concentration; CI, confidence interval; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; n, number of experiments; ND, no data; NIR, nirmatrelvir; SI, selectivity index (CC_{50} value/EC_{50} value)

NIR and Ritonavir Activity Against SARS-CoV-2 WA1/2020 in A549-ACE2 Cells (Pfizer 2022i)

The activity of NIR, ritonavir, and NIR + ritonavir against SARS-CoV-2 was investigated in A549-ACE2 cells using a luciferase reporter assay. A549-ACE2 cells are human alveolar epithelial cells engineered to stably express human angiotensin converting enzyme-2 (ACE2), the receptor for SARS-CoV-2. These experiments were performed using a recombinant SARS-CoV-2 (USA-WA1/2020-based) reporter virus that encodes NanoLuc luciferase (Promega) in place of ORF7 (Xie et al. 2020b). Cells were infected at an MOI of ~0.01, and compounds were added 10 minutes post-infection. NIR and ritonavir alone were tested at final concentrations of 0.1 to 3,000 nM. In NIR+ritonavir combination experiments, NIR was tested at concentrations of 15 to 3,000 nM, and ritonavir was tested at concentrations of 176 to 3,000 nM. These experiments were performed in the absence of CP-100356 (P-gp inhibitor). Luciferase activity was measured at 72 hr post-infection. Cell viability was measured in uninfected cells treated with NIR or ritonavir in parallel using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). NIR inhibited SARS-CoV-2 replication with geometric mean EC_{50} and EC_{90} values of 77.9 and 215 nM, respectively (Table 217), similar to the geometric mean EC_{50} and EC_{90} values of 74.5 and 155 nM observed in Vero E6 cells treated with CP-100356.

These findings indicate that A549-ACE2 cells express low levels of P-gp. NIR was not cytotoxic at the maximum concentration tested (3,000 nM), resulting in an SI value >38.5. Ritonavir alone had no antiviral activity or cytotoxicity up to the maximum concentration tested (3,000 nM). In NIR + ritonavir combination experiments, NIR alone had an EC_{50} value of 233 nM. In the presence of ritonavir, NIR had EC_{50} values ranging from 151 to 450 nM (Table 218). There was no clear concentration-dependent effect of ritonavir on NIR activity, although a small decrease in NIR activity was observed at the highest concentrations of ritonavir tested (2,000 to 3,000 nM). Combination cytotoxicity was not measured. Overall, these results indicate that ritonavir does not have activity against SARS-CoV-2 in the absence or presence of NIR.

Table 217. Activity of NIR Alone and Ritonavir Alone Against SARS-CoV-2 in A549-ACE2 Cells (Without P-gp Inhibitor)

NIR				Ritonavir		
Geomean EC_{50} nM (95% CI)	Geomean EC_{90} nM (95% CI)	Geomean CC_{50} nM	SI	Geomean EC_{50} nM	Geomean EC_{90} nM	Geomean CC_{50} nM
77.9 (50.5-120), n=28	215 (146 to 317), n=28	>3,000, n=14	>38.5	>3,000, n=2	>3,000, n=2	>3,000, n=1

Source: Adapted from (Pfizer 2022i), p. 15.
Abbreviations: CC_{50}, 50% cytotoxic concentration; CI, confidence interval; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; n, number of experiments; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, selectivity index (CC_{50} value/EC_{50} value)

Table 218. Activity of NIR + Ritonavir Against SARS-CoV-2 in A549-ACE2 Cells (Without P-gp Inhibitor)

Ritonavir (nM)	NIR EC_{50} (nM)	Lower 95% CI (nM)	Upper 95% CI (nM)
0	233	202	268
176	168	140	202
263	185	157	216
395	201	183	221
593	262	216	318
889	151	132	173
1,330	161	125	207
2,000	336	296	380
3,000	450	379	534

Source: Adapted from , (Pfizer 2022i) p. 18.
Abbreviations: CI, confidence interval; EC_{50}, half maximal effective concentration; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 in Differentiated Normal Human Bronchial Epithelial (dNHBE) Cells (Pfizer 2021g)

The activity of NIR against SARS-CoV-2 (USA-WA1/2020) was further investigated in dNHBE cells (MatTek EpiAirway). According to the manufacturer, EpiAirway is a 3-dimensional mucociliary tissue model consisting of dNHBE cells cultured at the air-liquid interface. The model exhibits human-relevant tissue structure and cell morphology and consists of organized keratin 5-positive basal cells, mucus-producing goblet cells, functional tight junctions, and beating cilia. The dNHBE cells used by the Applicant were derived from a single donor, who was a 23-year-old, healthy, non-smoking, Caucasian male. Cells were infected at an MOI of ~0.001, and NIR was added at the time of infection. Depending on the experiment, NIR was tested at concentrations of 10 to 10,000 nM, 10 to 500 nM, or 8 to 5,000 nM. These experiments were performed in the absence of CP-100356 (P-gp inhibitor). Virus was applied to the apical side, while NIR was added to the apical and basal sides of the cultures. Following an initial 2 hr incubation with virus and NIR, the apical medium was removed, and the basal medium was replaced with fresh NIR-containing medium. The cells were then maintained at the air-liquid interface, and viruses in the apical compartment were harvested 3- and 5-days post-infection by washing the surface with pre-warmed culture medium. Virus titers in apical washes (expressed as $TCID_{50}$/mL) were then determined by CPE assay in Vero 76 cells. Three independent experiments were performed. NIR had activity against SARS-CoV-2 in dNHBE cells with geometric mean EC_{50} and EC_{90} values of 32.6-61.8 nM and 56.1-181 nM, respectively

(Table 219). These values are similar to those reported in Vero E6 (+CP-100356) and A549-ACE2 (-CP-100356) cells.

Table 219. Activity of NIR Against SARS-CoV-2 in dNHBE Cells (Without P-gp Inhibitor)

	EC_{50} (nM)				EC_{90} (nM)			
Virus Collection Day	N=1	N=2	N=3	Geomean (95% CI)	N=1	N=2	N=3	Geomean (95% CI)
3	75.7	67.8	46.1	61.8 (32.4 - 118)	157	141	268	181 (76.9 - 425)
5	55.5	23.1	27.1	32.6 (10.2 - 104)	92.4	43.6	44.0	56.1 (19.2 - 164)

Source: Adapted from (Pfizer 2021g), p. 14.
CI, confidence interval; dNHBE, differentiated normal human bronchial epithelial cells; EC_{50}, half-maximal effective concentration; Geomean, geometric mean; N, replicate number; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Variants in Vero E6 P-gp Knockout and Vero E6-TMPRSS2 Cells (Pfizer 2022e; Pfizer 2022k)

The activity of NIR against SARS-CoV-2 variants was determined in Vero E6 P-gp knockout and Vero E6-TMPRSS2 cells. Vero E6 P-gp knockout cells were generated by the Applicant (details not provided). Vero E6-TMPRSS2 cells were obtained from (b) (4) and stably express human transmembrane protease serine 2 (TMPRSS2), a cellular protease involved in SARS-CoV-2 entry (Hoffmann et al. 2020). Vero E6-TMPRSS2 cells are known to be more susceptible to SARS-CoV-2 infection than Vero E6 cells (Matsuyama et al. 2020). In total, 10 SARS-CoV-2 isolates were tested in at least one cell line: USA-WA1/2020, Alpha, Beta (x2), Gamma, Delta, Lambda, Mu, Omicron BA.1, and Omicron BA.2. Some of these isolates had polymorphisms in M^{pro} (Table 220), but none had polymorphisms in any M^{pro} cleavage sites. In Vero E6 P-gp knockout cells, NIR activity was tested by CPE reduction and qRT-PCR assays, whereas only CPE reduction assay was performed in Vero E6-TMPRSS2 cells. In Vero E6-TMPRSS2 cells, NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). For the CPE reduction assay, cells were infected at MOIs of 0.03 to 0.04, and NIR was added at the time of infection. CPE reduction was measured 72 hr post-infection using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). For the qRT-PCR assay, cells were infected at an MOI of 0.04, and compounds were added at the time of infection. Cells were lysed 48 hr post-infection, and intracellular SARS-CoV-2 RNA levels were measured by qRT-PCR of nsp10.

In these assays, NIR inhibited SARS-CoV-2 USA-WA1/2020 replication with geometric mean EC_{50} values of ~32 to 96 nM (Table 220), similar to the values reported in other cell types. NIR had activity against all tested SARS-CoV-2 variants. Two Beta isolates had 3.0- to 4.4-fold reduced susceptibility to NIR (based on geometric mean EC_{50} values) in some assays. Both isolates had the M^{pro} K90R polymorphism, and one isolate also had the M^{pro} P252L polymorphism, which has been associated with reduced NIR susceptibility in cell culture (Iketani et al. 2023). The K90R substitution did not affect NIR activity in a biochemical assay or in cell culture when engineered into recombinant SARS-CoV-2 (see below). NIR retained activity against the Omicron BA.1 and BA.2 variants (geometric mean EC_{50} value fold-changes ≤1.1).

Table 220. NIR Activity Against SARS-CoV-2 Variants in Vero E6 P-gp Knockout and Vero E6-TMPRSS2 Cells

		Vero E6 P-gp Knockout (CPE)			Vero E6-TMPRSS2 With P-gp Inhibitor (CPE)			Vero E6 P-gp Knockout (qRT-PCR)		
Variant	M^{pro} Polymorphs	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	EC_{50} FC
WA1/2020 (n=3)	N/A	96.3 (86.7–110)	195 (174–225)	N/A	71.2 (51.7–92.1)	147 (105–191)	N/A	32.2 (15.6–90.6)	371 (311–463)	N/A
B.1.1.7 Alpha (n=3)	none	75.3 (58.7–90.5)	186 (172–199)	0.8	170 (145–182)	364 (309–399)	2.4	41.0 (39.1-45.2)	213 (106–595)	1.3
B.1.351 Beta (n=4)	K90R	ND	ND	ND	ND	ND	ND	141 (103-272)	533 (276-757)	4.4[a]
B.1.351 Beta (n=3-4)	K90R, P252L	171 (138–207)	363 (288–441)	1.8	217 (175–243)	460 (378–517)	3.0[a]	127.2 (39.8–220)	456 (344–683)	4.0[a]
P.1 Gamma (n=3)	none	87.7 (68.2–121)	222 (187–251)	0.9	204 (137–250)	430 (287–533)	2.9	24.9 (15.8–33.0)	153 (107–209)	0.78
B.1.617.2 Delta (n=2-3)	none	ND	ND	ND	82.2 (71.0–98.2)	168 (147–205)	1.2	15.9 (8.7–37.0)	26.0b (18.2–33.7)	0.5
C.37 Lambda (n=3-4)	G15S	59.5 (51.2–66.6)	171 (129–297)	0.6	93.0 (87.3–97.7)	193 (181–203)	1.3	21.2 (12.2–30.8)	127 (60.2–482)	0.7
B.1.621 Mu (n=3)	none	65.1 (62.0-68.5)	134 (129-139)	0.7	138 (101-203)	292 (212-427)	1.9	25.7 (21.9-30.2)	57.4 (51.4-69.2)	0.8
Omicron BA.1 (n=3)	P132H	ND	ND	ND	ND	ND	ND	16.2 (9.4-30.5)	ND	0.5
Omicron BA.2 (n=3)	P132H	ND	ND	ND	79 (63-98)	150 (125-185)	1.1	ND	ND	ND

Source: Adapted from (Pfizer 2022e), p. 14 and (Pfizer 2022k), p. 16-17.
[a.] EC_{50} value fold-changes ≥3.
[b.] Mathematic average, not geomean.
Abbreviations: CPE, cytopathic effect; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; FC, fold change relative to WA1/2020; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; ND, not determined; NIR, nirmatrelvir; P-gp, P-glycoprotein; Polymorphs, polymorphisms; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Subsequently, the Applicant determined the activity of NIR against SARS-CoV-2 USA-WA1/2020, BA.2, BA.2.12.1, BA.4, and BA.5 variants in Vero E6-TMPRSS2 cells by qRT-PCR assay of intracellular SARS-CoV-2 RNA. Relative to USA-WA1/2020, the BA.2, BA.2.12.1, BA.4, and BA.5 isolates contained the M^{pro} P132H polymorphism, but none of the isolates had any other polymorphisms in M^{pro} or M^{pro} cleavage sites. NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). Cells were infected at an MOI of 0.04, with compounds added at the time of infection. Cells were lysed 48 hr post-infection, and intracellular SARS-CoV-2 RNA levels were determined by qRT-PCR. NIR retained activity against the SARS-CoV-2 Omicron sub-variants BA.2, BA.2.12.1, BA.4, and BA.5, with fold-changes in geometric mean EC_{50} and EC_{90} values <1 relative to USA-WA1/2020 (Table 221).

Table 221. NIR Activity Against SARS-CoV-2 Omicron Subvariants in Vero E6-TMPRSS2 Cells (With P-gp Inhibitor)

Variant	M^{pro} Polymorphs	n	Geomean EC_{50} (nM) Range	EC_{50} Fold-Change	Geomean EC_{90} (nM) Range	EC_{90} Fold-Change
USA-WA1/2020	N/A	7	70 (49 – 98)	N/A	211 (123 – 478)	N/A
Omicron BA.2	P132H	5	65 (52 – 78)	0.9	132 (95 – 162)	0.6
Omicron BA.2.12.1	P132H	5	40 (34 – 44)	0.6	114 (72 – 408)	0.5
Omicron BA.4	P132H	3	39 (19 – 54)	0.6	98 (92 – 104)	0.5
Omicron BA.5	P132H	5	44 (29 – 117)	0.6	178 (109 – 451)	0.8

Source: Adapted from (Pfizer 2022k), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; P-gp, P-glycoprotein; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Variants in Vero-TMPRSS2 and HeLa-ACE2 Cells (Pfizer 2022d)

The activity of NIR against SARS-CoV-2 variants was also determined in Vero-TMPRRS2 and HeLa-ACE2 cells. Both cell lines were obtained from (b) (4) Vero-TMPRRS2 are Vero cells stably expressing human TMPRSS2, while HeLa-ACE2 cells are HeLa (human cervical carcinoma) cells stably expressing human ACE2. In total, 6 variants were tested: USA-WA1/2020, mouse-adapted (MA) WA1/2020, Alpha, Beta, Delta, and Omicron BA.1. Relative to USA-WA1/2020, the Beta and BA.1 isolates contained the M^{pro} K90R and P132H polymorphisms, respectively, but none of the isolates had any other polymorphisms in M^{pro} or M^{pro} cleavage sites. Cells were infected at MOIs of 0.025 (Vero-TMPRSS2) or 0.25 (HeLa-ACE2), with NIR added 2 hr before infection. In Vero-TMPRSS2 cells, NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). Cells were incubated for 48 hr, washed, fixed, and immunostained for the SARS-CoV-2 nucleocapsid (N) protein. The percentages of infected cells were determined using a Celigo imaging cytometer (Nexcelom). The effect of NIR on cell viability in uninfected cells was examined in parallel by MTT assay (Roche). NIR had activity against all SARS-CoV-2 variants (Table 222). In Vero-TMPRSS2 cells, the Beta isolate had 3.2-fold reduced susceptibility to NIR (based on EC_{50} value). NIR was not cytotoxic up to

the maximum concentration tested (10,000 nM), resulting in SI values of >82.6->588 in Vero-TMPRSS2 cells and >44.4->143 in HeLa-ACE2 cells.

Table 222. NIR Activity Against SARS-CoV-2 Variants in Vero-TMPRSS2 and HeLa-ACE2 Cells

		Vero-TMPRSS2 (+CP-100356, n=1)				HeLa-ACE2 (-CP-100356, n=2)			
Variant	M^{pro} Polymorphs	EC_{50} (nM)	EC_{90} (nM)	EC_{50} Fold-Change	CC_{50}	Mean EC_{50} (nM)	Mean EC_{90} (nM)	EC_{50} Fold-Change	CC_{50}
WA1/2020	N/A	38	45	N/A	>10,000	207	802	N/A	>10,000
MA WA1/2020	none	17	34	0.5	>10,000	128	275	0.6	>10,000
B.1.1.7 Alpha	none	22	49	0.6	>10,000	118	236	0.6	>10,000
B.1.351 Beta	K90R	121	138	3.2[a]	>10,000	225	762	1.1	>10,000
B.1.617.2 Delta	none	73	133	1.9	>10,000	169	1,134	0.8	>10,000
Omicron BA.1	P132H	23	51	0.6	>10,000	70	203	0.3	>10,000

Source: Adapted from (Pfizer 2022d), p. 12.
[a.] EC_{50} value fold-change ≥3.
Abbreviations: CC_{50}, 50% cytotoxic concentration; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; n, number of experiments; N/A, not applicable; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

NIR Activity Against SARS-CoV-2 Delta Clinical Isolates in Vero E6-TMPRSS2 Cells (Pfizer 2022f)

In this report, the Applicant determined the activity of NIR against 4 clinical isolates of the SARS-CoV-2 Delta variant in Vero E6-TMPRSS2 cells treated with 2,000 nM CP-100356 (P-gp inhibitor). NIR retained activity against the 4 Delta isolates, with geometric mean EC_{50} value fold-changes ≤2.1 compared to the control virus (WA1/2020).

NIR Activity Against Other Human CoVs in Cell Culture (Pfizer 2021f; Pfizer 2021e; Pfizer 2021c)

The activity of NIR against 3 other human coronaviruses was determined in cell culture: SARS-CoV-1, MERS-CoV, and HCoV-229E. SARS-CoV-1 and MERS-CoV are betacoronaviruses, like SARS-CoV-2, whereas HCoV-229E is an alphacoronavirus.

The activity of NIR against SARS-CoV-1 (Toronto-2) was determined in Vero E6 cells by CPE reduction assay in the absence and presence of 2,000 nM CP-100356 (P-gp inhibitor). In the absence of CP-100356, NIR inhibited SARS-CoV-1 replication with geometric mean EC_{50} and EC_{90} values of 12,300 and 25,500 nM, respectively. In the presence of CP-100356, NIR inhibited SARS-CoV-1 replication with geometric mean EC_{50} and EC_{90} values of 151 and 317 nM, respectively. These values are ~2.0 to 2.7-fold higher than those reported for SARS-CoV-2 (WA1/2020) in the same cell line. NIR was not cytotoxic in uninfected Vero E6 cells up to the maximum concentration tested (100,000 nM).

The activity of NIR against MERS-CoV (EMC/2012) was investigated in Vero 81 (STAT1 knockout) cells by CPE reduction assay in the absence and presence of 1,000 nM CP-100356 (P-gp inhibitor). In the absence of CP-100356, NIR inhibited MERS-CoV replication with geometric mean EC_{50} and EC_{90} values of 5,410 and 11,600 nM, respectively. In the presence of CP-100356, NIR inhibited MERS-CoV replication with geometric mean EC_{50} and EC_{90} values of 166 and 351 nM, respectively. NIR activity against SARS-CoV-2 was not determined in Vero 81 cells, but these values are ~1.2- to 2.3-fold higher than those reported for SARS-CoV-2

(WA1/2020) in Vero E6 cells (+CP-100356). NIR was not cytotoxic in uninfected Vero 81 cells up to the maximum concentration tested (100,000 nM).

The activity of NIR against HCoV-229E (ATCC VR-740) was investigated in MRC-5 (human fetal lung fibroblast) cells by CPE reduction assay in the absence of CP-100356. The Applicant previously demonstrated that the activity of another M^{pro} inhibitor (PF-00835231) against HCoV-229E in MRC-5 cells was not affected by CP-100356, indicating that this cell line expresses low levels of P-gp (Boras et al. 2021). NIR inhibited HCoV-229E replication with geometric mean EC_{50} and EC_{90} values of 190 and 620 nM, respectively. NIR activity against SARS-CoV-2 was not determined in MRC-5 cells, but these values are ~2.6-4.0-fold higher than those reported for SARS-CoV-2 (WA1/2020) in Vero E6 cells (+CP-100356). NIR was not cytotoxic in MRC-5 cells up to the maximum concentration tested (100,000 nM).

NIR Activity Against Human Picornaviruses in Cell Culture (Pfizer 2021b)

The activity of NIR against two human picornaviruses was determined in cell culture: enterovirus 71 (EV71, Shenzhen/120F1/09) and human rhinovirus 1B (HRV1B, ATCC VR-1645). Picornaviruses encode 3C proteases that are structurally related to coronavirus M^{pro}. NIR activity against EV71 and HRV1B was determined in human rhabdomyosarcoma and H1 HeLa cells, respectively, by CPE reduction assay. These experiments were performed in the absence of CP-100356. NIR did not inhibit EV71 or HRV1B replication at the maximum concentration tested (100,000 nM). NIR also did not have cytotoxicity in uninfected cells up to the maximum concentration tested (100,000 nM). These results indicate that the activity of NIR may be limited to coronaviruses. Positive controls for antiviral activity were not included.

Other Studies Related to NIR Antiviral Activity in Cell Culture

NIR retained activity against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Omicron BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and/or XBB variants in cell culture (Abdelnabi et al. 2022; Bojkova et al. 2022a; Bojkova et al. 2022b; Li et al. 2022; Ohashi et al. 2022; Saito et al. 2022; Takashita et al. 2022a; Takashita et al. 2022b; Takashita et al. 2022c; Vangeel et al. 2022; Imai et al. 2023). These findings indicate that NIR has broad activity against SARS-CoV-2 variants.

20.2.2. Antiviral Activity in Cell Culture in the Presence of Serum

The Applicant did not directly determine the impact of serum on NIR antiviral activity. However, in (Pfizer 2020b), the Applicant measured the binding of NIR (300 to 10,000 nM) to proteins in human, cynomolgus monkey, and rat plasma by equilibrium dialysis. NIR was found to be 67 to 70%, 50 to 61%, and 51 to 53% bound to proteins from human, cynomolgus monkey, and rat plasma, respectively. Based on these results and the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM), the Applicant estimated the plasma protein-adjusted EC_{90} value to be 585 nM (292 ng/mL), which was selected as the target plasma exposure (C_{min}) for clinical studies.

20.2.3. Antiviral Cytotoxicity/Selectivity Index

As described above, NIR did not have cytotoxicity in uninfected cells up to the maximum concentration tested in any cell type, resulting in CC_{50} values >3,000 nM in A549-ACE2 (-CP-100356) cells, >10,000 nM in Vero-TMPRSS2 (+CP-100356) and HeLa ACE2 (-CP-100356) cells, and >100,000 nM in Vero E6 (±CP-100356), Vero 81 (+CP-100356), MRC-5 (-CP-100356), human rhabdomyosarcoma (-CP-100356), and H1 HeLa (-CP-100356) cells. NIR had favorable selectivity index (SI) values (CC_{50} value/EC_{50} value) against SARS-CoV-2 of >38.5 (A549-ACE2, -CP-100356), >44.4->143 (HeLa-ACE2, -CP-100356), >82.6->588 (Vero-TMPRSS2, +CP-100356), and >1,250 (Vero E6, +CP-100356). NIR had favorable SI values against SARS-CoV-1, MERS-CoV, and HCoV-229E of >662 (Vero E6, +CP-100356), >602 (Vero 81, +CP-100356), and >526 (MRC-5, -CP-100356), respectively.

20.2.4. Combination Antiviral Activity in Cell Culture

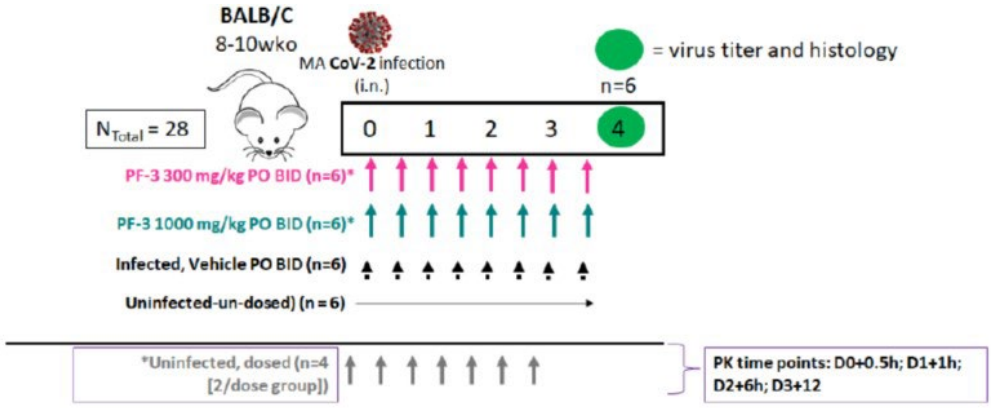
As described above, the Applicant investigated the activity of NIR in combination with ritonavir in A549-ACE2 cells. The Applicant did not provide reports on the activity of NIR in combination with other antivirals approved or authorized by the FDA for the treatment of COVID-19, such as remdesivir (Veklury) or molnupiravir (Lagevrio). However, NIR is not expected to have antagonistic activity with these products in cell culture as they have distinct targets. In Zhou et al., NIR and remdesivir did not have antagonistic activity against SARS-CoV-2 in cell culture (Zhou et al. 2022b). Likewise, in Gidari et al. and Rosenke et al., NIR and molnupiravir did not have antagonistic activity against SARS-CoV-2 in cell culture or in rhesus macaques, respectively (Gidari et al. 2022; Rosenke et al. 2023). Note that this does not rule out a potential effect of molnupiravir-mediated mutagenesis affecting NIR resistance development, given the random mutagenic effects of molnupiravir throughout the SARS-CoV-2 genome (FDA 2022a; FDA 2022b).

20.2.5. Antiviral Activity in Animal Models

NIR Activity in SARS-CoV-2 MA10-Infected BALB/c Mice (Pfizer 2021j)

The activity of NIR was evaluated against mouse-adapted (MA) SARS-CoV-2 MA10 in BALB/c mice in two independent studies. In BALB/c mice, SARS-CoV-2 MA10 causes severe, and in some cases lethal, lung disease (Leist et al. 2020). The extent of lethality depends on the infectious dose and age of the mice. SARS-CoV-2 MA10 does not encode any M^{pro} substitutions. In each study, 8-to-10-week-old female mice were inoculated intranasally with 10^5 $TCID_{50}$ of SARS-CoV-2 MA10 (Figure 106). NIR was orally administered twice daily (BID) at 300 or 1,000 mg/kg starting at 4 hours post-infection on Day 0 and continuing to Day 3. Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were weighed daily to measure infection-associated weight loss and were euthanized on Day 4 for determination of lung virus titers, histopathology, and immunohistochemistry. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected animals were treated with NIR for PK studies.

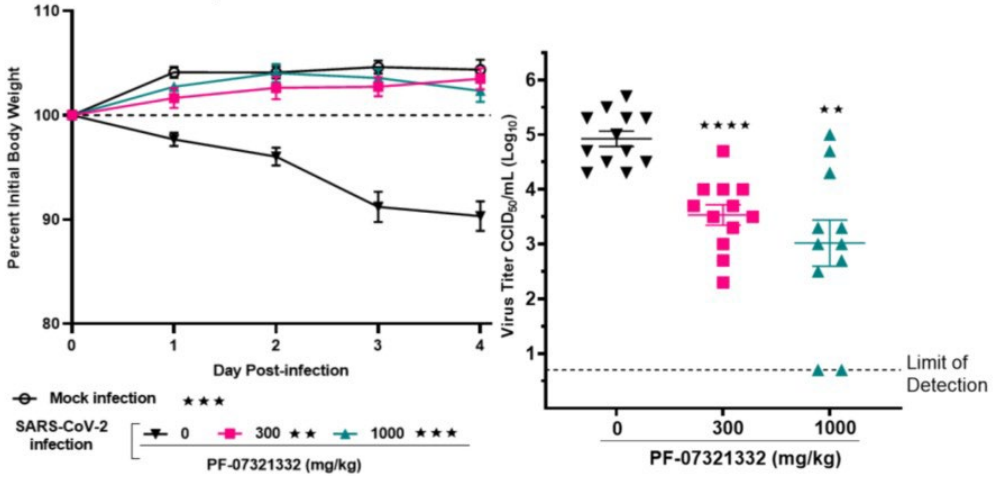
Figure 106. Experimental Design to Test Efficacy of NIR in SARS-CoV-2 MA10-Infected BALB/c Mice



Source: (Pfizer 2021j), p. 11.
Abbreviations: BID, twice daily; D, day; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; N_{total}, total number of animals; PF-3, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

Infected, vehicle-treated mice lost ~10% of their initial body weight through Day 4 (Figure 107). In contrast, uninfected mice and infected, NIR-treated mice gained body weight over the course of the experiment. In infected, vehicle-treated mice, the mean lung virus titer was 4.9 $\log_{10}$ $TCID_{50}$/mL on Day 4. In infected mice treated with NIR at 300 or 1,000 mg/kg BID, mean lung virus titers were 3.5 $\log_{10}$ and 3.0 $\log_{10}$ $TCID_{50}$/mL, respectively, on Day 4. Thus, NIR resulted in 1.4 $\log_{10}$ and 1.9 $\log_{10}$ reductions in mean lung virus titers at 300 or 1,000 mg/kg BID, respectively. Results were generally consistent between studies 1 and 2.

Figure 107. Effects of NIR on Bodyweight and Lung Virus Titers in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 1 and 2 Combined)

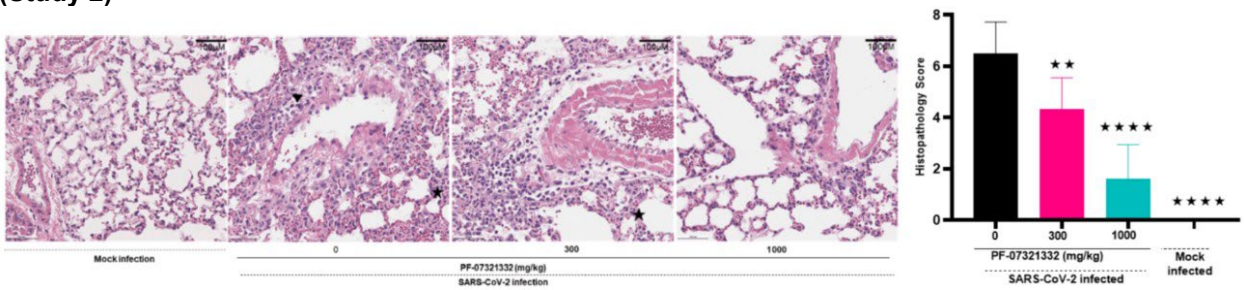


Source: (Pfizer 2021j), p. 27-28.
Note: p-values were determined by ANOVA with Dunnett's post-test, and values are relative to infected, vehicle-treated mice.
** indicates p <0.01
*** indicates p <0.001
**** indicates p <0.0001
Abbreviations: $CCID_{50}$, median cell culture infectious dose; PF-07321332, nirmatrelvir.

In study 1, lung histopathology analyses were inconclusive due to poor quality of samples from infected, vehicle-treated mice. In study 2, blinded assessments of lungs from infected, vehicle-

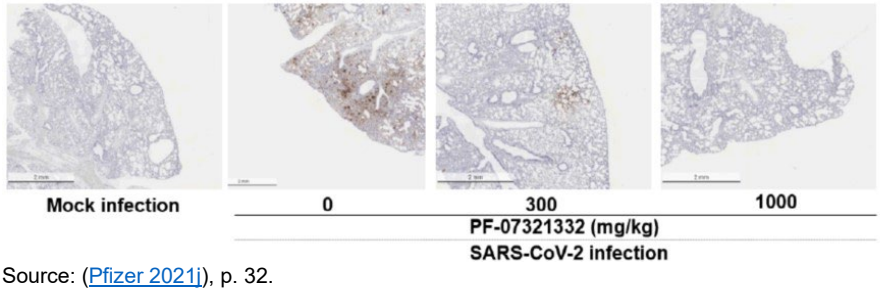
treated mice showed evidence of increased perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, cellular debris in alveolar lumen, alveolar inflammation, and thickening of the alveolar septum compared to infected, NIR-treated mice and uninfected mice. Most of the infected mice exhibited multifocal pulmonary lesions, but infected, NIR-treated mice developed significantly fewer lesions than infected, vehicle-treated mice (Figure 108). Thus, NIR reduced lung tissue damage through Day 4 due to virus replication and limited cellular infiltration. In addition, immunohistochemistry of lung sections was performed using an anti-SARS-CoV-2 nucleocapsid (N) antibody (Figure 109). NIR treatment resulted in dose-dependent decreases in N protein staining, showing that NIR reduced viral replication in the lungs on Day 4.

Figure 108. Effect of NIR on Lung Histopathology in SARS-CoV-2 MA10-Infected BALB/c Mice (Study 2)



Source: (Pfizer 2021j), p. 31-32.
Note: Left, Hematoxylin- and eosin-stained lung sections focusing on perivascular damage and alveolar inflammation. Right, lung histopathology scores.
Note: Four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: p-values were determined by one-way ANOVA with Dunnett's post-test, and values are relative to infected, vehicle-treated mice.
** indicates p <0.01
**** indicates p <0.0001
Abbreviations: NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 109. Effect of NIR on SARS-CoV-2 Nucleocapsid Staining in SARS-CoV-2 MA10-Infected BALB/c Mice (Study 2)



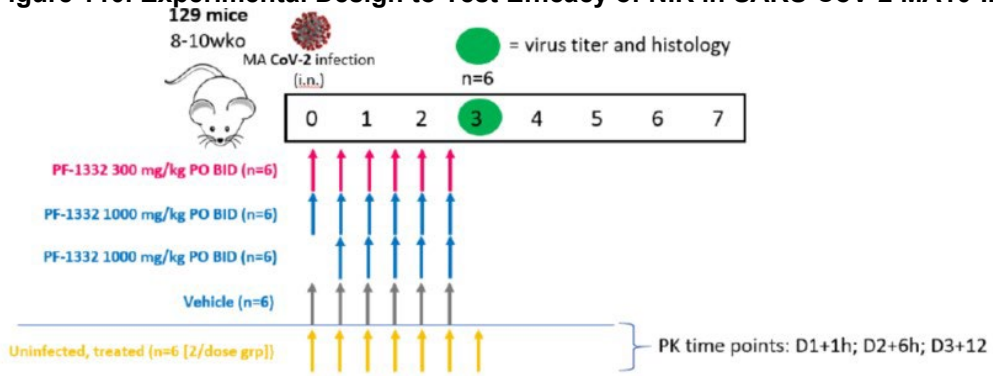
Source: (Pfizer 2021j), p. 32.
Note: Immunohistochemistry images indicating the presence of SARS-CoV-2 nucleocapsid protein (brown stain).
Abbreviations: NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

PK studies were also performed using a separate group of uninfected, NIR-treated animals. Minimal unbound plasma concentrations (C_{min}) of NIR at 12 hr post-last dose were 0.9x and 4.2x higher (for 300 and 1,000 mg/kg BID, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM). These results show that NIR has antiviral activity at C_{min} unbound plasma exposures $\geq EC_{90}$ value in BALB/c mice. However, the higher dose of NIR (1,000 mg/kg) had better activity.

NIR Activity in SARS-CoV-2 MA10-Infected 129 Mice (Pfizer 2021i)

The activity of NIR was also evaluated against SARS-CoV-2 MA10 in 129 mice, which are immunocompetent mice that are more susceptible to SARS-CoV-1 infection than BALB/c mice (Gretebeck and Subbarao 2015). Female 8-to-10-week-old mice were inoculated intranasally with $2.5x10^4$ pfu of SARS-CoV-2 MA10. NIR was orally administered at 300 or 1,000 mg/kg BID starting at 4 hr (300 or 1,000 mg/kg) or 12 hr (1,000 mg/kg) post-infection on Day 0 and continuing to Day 2 (Figure 110). Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were weighed daily to measure infection-associated weight loss and were euthanized on Day 3 for determination of lung virus titers and histopathology. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected animals were treated with NIR for PK studies.

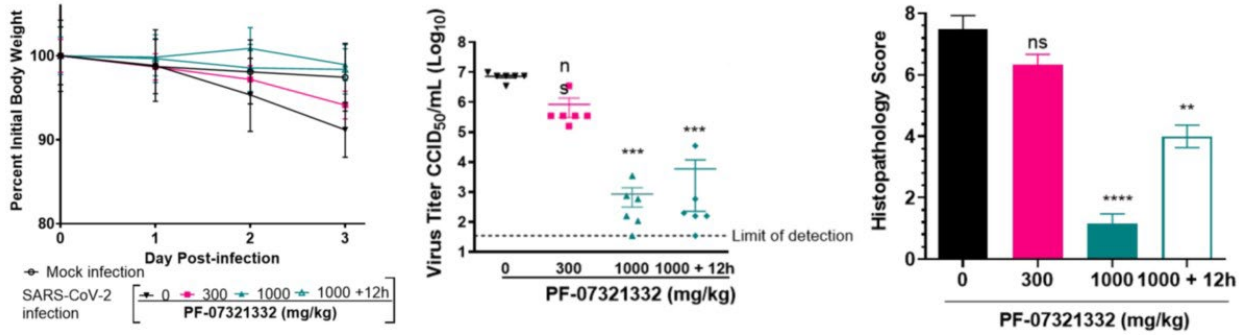
Figure 110. Experimental Design to Test Efficacy of NIR in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 9.
Abbreviations: BID, twice daily; D, day; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; PF-1332, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

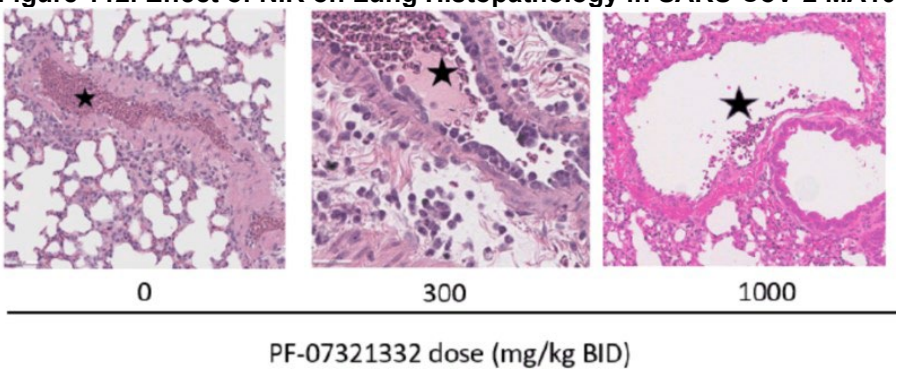
In this study, infected vehicle-treated mice lost ~9% bodyweight by Day 3 (Figure 111). NIR prevented weight loss at the 1,000 mg/kg dose, although the Applicant did not indicate whether these findings were statistically significant. The mean lung virus titer in infected, vehicle-treated mice was 6.8 log_{10} $TCID_{50}$/mL on Day 3. NIR resulted in 1.1 log and 4.2 to 4.3 log_{10} reductions in mean lung virus titers at 300 and 1,000 mg/kg BID, respectively, although only the results with the 1,000 mg/kg dose were statistically significant. Lastly, NIR at 1,000 mg/kg resulted in reduced lung histopathology in blinded assessments on Day 3, especially when treatment was initiated at 4 hr post-infection (Figure 111 and Figure 112).

Figure 111. Effects of NIR on Bodyweight, Lung Virus Titers, and Lung Histopathology in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 17-19.
Note: For lung histopathology, four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: vehicle-treated mice. p-values were determined by Kruskal-Wallis test and relative to vehicle-treated mice.
** indicates p <0.01
*** indicates p <0.001
**** indicates p <0.0001
Abbreviations: $CCID_{50}$, median cell culture infectious dose; h, hour; log, logarithm; NIR, nirmatrelvir; ns, not significant; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 112. Effect of NIR on Lung Histopathology in SARS-CoV-2 MA10-Infected 129 Mice



Source: (Pfizer 2021i), p. 19.
Note: Representative histopathology images using hematoxylin and eosin staining depicting perivascular inflammation from the untreated/infected 0 mg/kg control, 300 mg/kg BID and 1000 mg/kg BID treatment groups.
Abbreviations: BID, twice daily; NIR, nirmatrelvir; PF-07321332, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

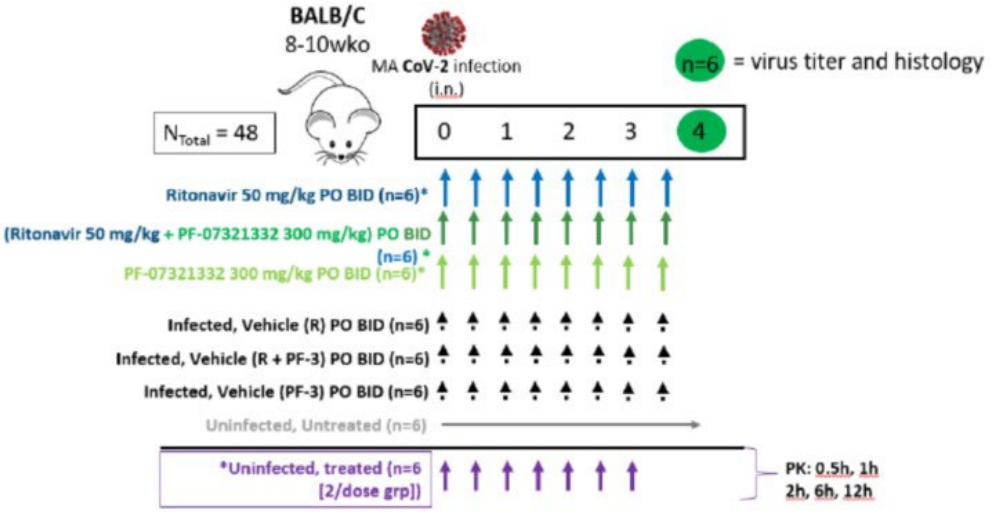
PK studies were also performed using a separate group of uninfected, NIR-treated animals. Minimal unbound plasma concentrations (C_{min}) of NIR at 12 hr post-last dose were 3.5× and 25× higher (for 300 and 1,000 mg/kg BID, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM).

NIR + Ritonavir Activity in SARS-CoV-2 MA10-Infected BALB/c Mice (Pfizer 2022m)

The activity of NIR, ritonavir, and NIR+ritonavir was evaluated against SARS-CoV-2 MA10 in BALB/c mice in two independent studies. In each study, 8-to-10-week-old female mice were inoculated intranasally with 10^5 $TCID_{50}$ of SARS-CoV-2 MA10 (Figure 113). Mice were orally treated with NIR (300 mg/kg BID), ritonavir (50 mg/kg BID), or NIR+ritonavir (300 mg/kg BID and 50 mg/kg BID, respectively) starting at 4 hours post-infection on Day 0 and continuing to

Day 3. Thus, dosing modeled prophylaxis, not treatment of symptomatic disease. Mice were euthanized on Day 4 for determination of lung virus titers, histopathology, and immunohistochemistry. Virus titers ($TCID_{50}$/mL) were determined by CPE assay in Vero 76 cells. With this experimental design, mice were not followed for a sufficient duration to assess the impact of NIR through the full course of disease. Uninfected, untreated and infected, vehicle-treated mice were included as controls. In addition, uninfected were treated with NIR, ritonavir, or NIR+ritonavir for PK studies.

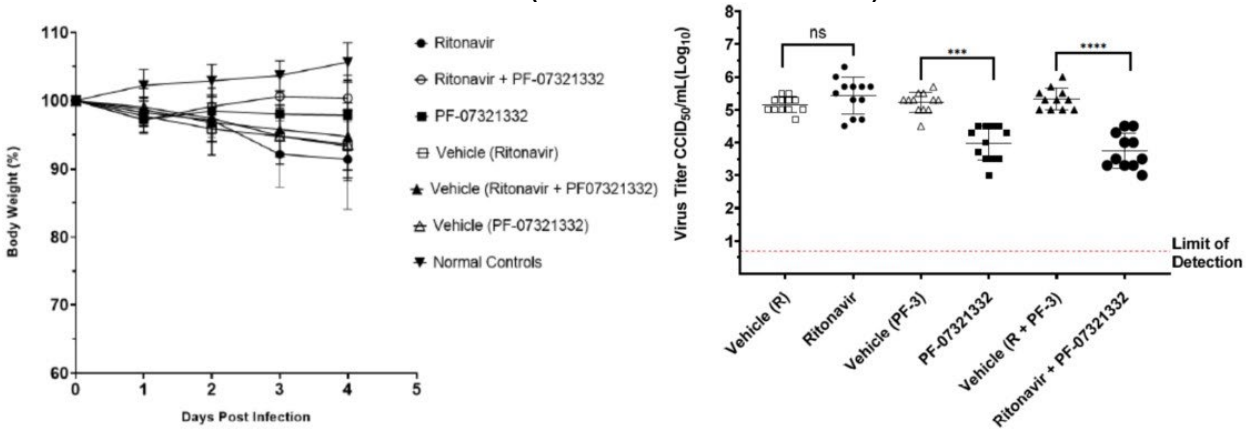
Figure 113. Experimental Design to Test Efficacy of NIR, Ritonavir, and NIR + Ritonavir in SARS-CoV-2 MA10-Infected BALB/c Mice



Source: (Pfizer 2022m), p. 10.
Abbreviations: BID, twice daily; h, hour; i.n., intranasal; MA, mouse-adapted; n, number of animals; NIR, nirmatrelvir; N_{total}, total number of animals; PF-3/PF-07321332, nirmatrelvir; PK, pharmacokinetics; PO, dosed orally; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wko, weeks old

Infected mice treated with ritonavir alone or vehicle lost ~10% of their initial body weight through Day 4, while uninfected mice gained body weight over the course of the experiment (Figure 114). Infected mice treated with NIR or NIR+ritonavir lost less weight than those treated with ritonavir or vehicle, although the Applicant did not indicate whether these findings were statistically significant. In vehicle-treated mice, mean lung virus titers were 5.2-5.3 log_{10} $TCID_{50}$/mL on Day 4. In ritonavir-treated mice, the mean lung virus titer was 5.4 log_{10} $TCID_{50}$/mL; thus, ritonavir alone did not have antiviral activity. In NIR-treated mice, the mean lung virus titer was 4.0 log_{10} $TCID_{50}$/mL; thus, NIR alone resulted in a 1.2 log_{10} reduction in virus titer relative to vehicle control. In mice treated with NIR + ritonavir, the mean lung virus titer was 3.7 log_{10} $TCID_{50}$/mL; thus, NIR + ritonavir resulted in a 1.6 log_{10} reduction in virus titer relative to vehicle control. The Applicant did not indicate whether the difference in lung viral titers between NIR and NIR + ritonavir was statistically significant. Results were generally consistent between the two studies.

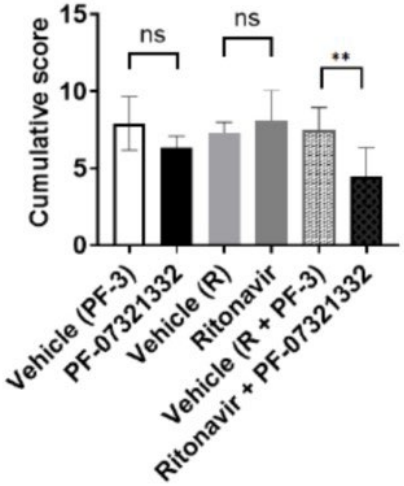
Figure 114. Effects of NIR, Ritonavir, and NIR + Ritonavir on Body Weight and Lung Virus Titers in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 2 and 3 Combined)



Source: (Pfizer 2022m), p. 27, 30.
Note: p-values were determined by non-parametric one-way ANOVA with Kruskal-Wallis post-test.*** indicates p <0.001 and **** indicates p <0.0001 relative to infected vehicle-treated mice.
Abbreviations: CCID50, median cell culture infectious dose; log, logarithm; NIR, nirmatrelvir; ns, not significant; PF-3/PF-07321332, nirmatrelvir; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In contrast to results from report 105036, NIR alone did not reduce mean lung histopathology scores in blinded assessments on Day 4 in this study (Figure 115). Ritonavir alone did not affect mean lung histopathology scores either. However, NIR+ritonavir significantly reduced the mean lung histopathology score. The Applicant also provided representative lung histopathology and immunohistochemistry images for studies 2 and 3 (data not shown).

Figure 115. Effects of NIR, Ritonavir, and NIR + Ritonavir on Lung Histopathology Scores in SARS-CoV-2 MA10-Infected BALB/c Mice (Studies 2 and 3 Combined)



Source: (Pfizer 2022m), p. 33.
Note: Four parameters were evaluated in a blinded manner with a 5-point scoring system: perivascular inflammation, bronchial or bronchiolar epithelial degeneration or necrosis, bronchial or bronchiolar inflammation, and alveolar inflammation.
Note: p-values were determined by non-parametric one-way ANOVA with Kruskal-Wallis post-test.
** indicates p <0.01.
Abbreviations: NIR, nirmatrelvir; ns, not significant; PF-3/PF-07321332, nirmatrelvir; R, ritonavir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

PK studies were also performed using a separate group of uninfected, treated animals. In study 2, minimal unbound plasma concentrations (C_{min}) of NIR at 12 hours post-last dose were 0.9x and

8x higher (for NIR and NIR + ritonavir, respectively) than the EC_{90} value of NIR against SARS-CoV-2 in dNHBE cells (181 nM). In study 3, C_{min} values at 12 hours post-last dose were 2.9x and 28x higher (for NIR and NIR + ritonavir, respectively) than the EC_{90} value. These results show that ritonavir significantly increased NIR plasma exposures in BALB/c mice.

Other Studies Related to NIR Antiviral Activity in Animal Models

In Abdelnabi et al., NIR was shown to have antiviral activity in Syrian hamsters infected with the SARS-CoV-2 Beta or Delta variants (Abdelnabi et al. 2022). In addition, NIR prevented transmission of SARS-CoV-2 Delta from infected, NIR-treated hamsters to co-housed, uninfected hamsters. NIR dosing (125-250 mg/kg BID) was initiated at the time of infection in these experiments. In Uraki et al., NIR was shown to have antiviral activity in Syrian hamsters infected with the SARS-CoV-2 Omicron BA.2 variant. NIR dosing (1,000 mg/kg BID) was initiated 24 hours post-infection (Uraki et al. 2022).

20.3. Drug Resistance

20.3.1. Resistance Development in Cell Culture

Selection of NIR-Resistant MHV in Cell Culture (Pfizer 2021a)

To identify M^{pro} residues associated with NIR resistance, the Applicant initially selected for NIR resistance in cell culture using mouse hepatitis virus (MHV) A59 (ATCC VR-764), a betacoronavirus used as a surrogate for SARS-CoV-2. In L929 (mouse fibroblast) cells, NIR inhibited MHV replication in a CPE reduction assay with EC_{50} values of 847 and 395 nM in the absence and presence of 2,000 nM CP-100356 (P-gp inhibitor), respectively. These results indicate that NIR may have reduced activity against MHV M^{pro} relative to SARS-CoV-2 M^{pro}, in agreement with a published study (Heilmann et al. 2023). Overall, MHV M^{pro} and SARS-CoV-2 M^{pro} have ~51% amino acid identity. In addition, MHV M^{pro} has several amino acid differences near the NIR binding site relative to SARS-CoV-2 M^{pro}, including N142C, H164Q, M165L, P168S, V186R, R188A, T190V, and A191V. Thus, the extent to which NIR resistance substitutions in MHV are predictive of resistance substitutions in SARS-CoV-2 is unclear.

To select for NIR resistance, MHV was serially passaged 11× in L929 cells with increasing concentrations of NIR. This experiment was performed in the absence of CP-100356. The initial MOI was 0.001 (specific number of infectious units unknown), and the initial concentration of NIR was 420 nM, which represents ~0.5xEC_{50} value (847 nM). The final concentration of NIR was 42,340 nM, which represents ~50xEC_{50} value. This experiment was performed using a single virus stock. Each passage lasted 2 to 3 days, and the virus titer was determined after each passage by plaque assay in L929 cells. MOIs varied among passages from 0.001 to 1.1. M^{pro} and M^{pro} cleavage site substitutions were identified by whole-genome Illumina sequencing of viral RNA from passages 2-9 and 33 plaque-purified viruses (13 from passage 9, 20 from passage 10). Virus titer was not detected after passage 11.

In viruses from passages 2 to 9, 4 M^{pro} substitutions were detected at a frequency >3%: P55L, S144A, F213L, and A250V (Table 223). In SARS-CoV-2 M^{pro}, the residues at these positions are E55, S144, I213, and P252, respectively. In addition, one substitution (ORF1ab S4470N) was

observed in an M^{pro} cleavage site at passage 2 but not in any later passages. The frequencies of these substitutions were not provided. Of the plaque-purified viruses, all 33 viruses contained the M^{pro} P55L and S144A substitutions (Table 224). In addition, 3 viruses contained other low-frequency (3-5%) M^{pro} substitutions: one with P15A, one with T50K and T129M, and one with F126L. In SARS-CoV-2 M^{pro}, the residues at these positions are G15 (P15A), L50 (T50K), Y126 (F126L), and A129 (T129M). The F213L and A250V M^{pro} substitutions were not detected in any of the plaque-purified viruses. None of the plaque-purified viruses had substitutions in M^{pro} cleavage sites.

Table 223. Sequencing of MHV Passaged in the Presence of NIR

Passage	NIR nM (×EC_{50})	MHV M^{pro} Substitutions ≥3%
2	850 (1)	F213L, A250V
3	1,060 (1.25)	P55L, F213L, A250V
4	2,120 (2.5)	P55L, F213L, A250V
5	2,540 (3)	P55L, F213L, A250V
6	3,390 (4)	P55L, F213L, A250V
7	4,230 (5)	P55L, F213L, A250V
8	8,470 (10)	P55L, F213L, A250V
9	25,410 (30)	P55L, S144A, F213L, A250V

Source: Adapted from (Pfizer 2021a), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; MHV, murine hepatitis virus; M^{pro}, main protease; NIR, nirmatrelvir

Table 224. Sequencing of Plaque-Purified MHV Passaged in the Presence of NIR

Passage	NIR nM (×EC_{50})	# of Plaques	MHV M^{pro} Substitutions ≥3% (# Plaques)
9	25,410 (30)	13	T50K (1/13), P55L (13/13), T129M (1/13), S144A (13/13)
10	33,870 (40)	20	P15A (1/20), P55L (20/20), F126L (1/20), S144A (20/20)

Source: Adapted from (Pfizer 2021a), p. 17-18.
Abbreviations: EC_{50}, half-maximal effective concentration; MHV, murine hepatitis virus; M^{pro}, main protease; NIR, nirmatrelvir

For 4 plaque-purified viruses, virus titers and susceptibility to NIR were determined (Table 225). Virus titers were determined in the absence of NIR by plaque assay in L929 cells. NIR activity was determined in the presence of 2,000 nM CP-100356 by qRT-PCR assay in L929 cells. All 4 viruses contained M^{pro} P55L and S144A substitutions. One virus also contained a low-frequency (3-5%) P15A substitution, while another virus contained low-frequency (3-5%) T50K and T129M substitutions. All 4 viruses had reduced susceptibility to NIR, with 4.4 to 4.9-fold higher EC_{50} values relative to the parental virus. These results indicate that the M^{pro} P55L and/or S144A substitutions likely confer reduced susceptibility to NIR. These results do not rule out the possibility that the other substitutions (e.g., P15A, T50K, F126L, and T129M) further enhance resistance, as these substitutions were present at low frequencies (3 to 5%). The Applicant did not confirm these results with recombinant viruses.

Table 225. Activity of NIR Against Plaque-Purified MHV With M^{pro} Substitutions

Passage	NIR nM (×EC_{50})	M^{pro} Substitutions	Titer (pfu/mL)	Titer FC	Geomean EC_{50} nM (Range)	EC_{50} FC
Parent Virus	N/A	N/A	1.5E+06	N/A	600 (400-1,000)	N/A
9	25,410 (30)	P55L, S144A	1.3E+05	12	2,630 (1,400-3,900)	4.4
9	25,410 (30)	T50K, P55L, T129M, S144A	1.3E+04	120	2,930 (2,000-4,500)	4.9
10	33,870 (40)	P55L, S144A	7.3E+04	21	2,650 (1,600-3,800)	4.4
10	33,870 (40)	P15A, P55L, S144A	2.5E+04	60	2,800 (1,600-4,400)	4.7

Source: Adapted from (Pfizer 2021a), p. 16.
Abbreviations: EC_{50}, half-maximal effective concentration; FC, fold-change; Geomean, geometric mean; M^{pro}, main protease; MHV, murine hepatitis virus; N/A, not applicable; NIR, nirmatrelvir; pfu, plaque-forming units.

In total, 8 M^{pro} substitutions were observed in NIR-selected MHV: P15A, T50K, P55L, F126L, T129M, S144A, F213L, and A250V. In SARS-CoV-2 M^{pro}, the residues at these positions are G15, L50, E55, Y126, A129, S144, I213, and P252, respectively. SARS-CoV-2 M^{pro} substitutions at some of these positions have been associated with NIR resistance in cell culture, including L50F, S144A, and P252L, usually in combination with other substitutions (see below, (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023)). In the SARS-CoV-2 M^{pro}/NIR co-crystal structure, none of these residues directly contact NIR, although S144 is located in close proximity (~3.6 Å).

Selection of NIR-Resistant SARS-CoV-2 in Vero E6 P-gp Knockout Cells (Pfizer 2022g)

In addition to MHV selection, the Applicant selected NIR-resistant SARS-CoV-2 (USA-WA1/2020) in Vero E6 P-gp knockout cells. SARS-CoV-2 was serially passaged 9 times under 5 different passaging schemes with constant or increasing NIR concentrations. In scheme #1, the NIR concentration was kept constant at 150 nM (1xEC_{50}). In schemes #2-4, the NIR concentration was progressively increased from 150 nM (1×EC_{50}) to either 1,314 nM (9xEC_{50}), 3,066 nM (21xEC_{50}), or 7,300 nM (50xEC_{50}). In scheme #5, the NIR concentration was kept constant at 370 nM (1xEC_{90}). These experiments were conducted using a single virus stock. In addition, for schemes #1-4, the first passage was the same (i.e., the virus was split after the first passage). Cells were infected at an MOI of 0.01 for the first passage and variable MOIs thereafter. Each passage lasted 2 to 8 days, depending on the amount of time required to generate >50% CPE in the culture. When sufficient CPE was detected, viral supernatants were collected and used to infect cells for the next passage. Virus titers ($TCID_{50}$/mL) after each passage were determined by CPE assay in Vero E6 P-gp knockout cells. Virus was passaged in the absence of NIR as a control.

After each passage, viral RNA was extracted, and M^{pro} and M^{pro} cleavage site substitutions with frequencies ≥3% were identified by whole-genome Illumina sequencing. In schemes #1-4, which shared the first virus passage, an M^{pro} T304I substitution was identified after passage 1 (Table 226). In scheme #1, T304I gradually increased in frequency, but no other M^{pro} substitutions were observed. In schemes #2-4, T304I increased in frequency more quickly, followed by acquisition of an A173V substitution, which increased to >90% frequency in a single passage. In scheme #3, L50F (20-21%) and T135I (6%) substitutions were also observed after passages 8 to 9. In scheme #5, T304I was identified first, followed by T21I and S144A substitutions. L50F (6%), T135I (7%), and A191V (5%) were also observed after passages 4 to 5 but not after later passages. Virus that was passaged in the absence of NIR did not acquire any

M^{pro} substitutions. In total, 7 distinct M^{pro} substitutions were identified: T21I, L50F, T135I, S144A, A173V, A191V, and T304I. In addition, the substitution frequencies indicate that some viruses had multiple M^{pro} substitutions, e.g., T21I+T304I, A173V+T304I, and T21I+S144A+T304I.

Table 226. Sequencing of SARS-CoV-2 Passaged in the Presence of NIR in Vero E6 P-gp Knockout Cells

	M^{pro} Substitutions ≥3% (Frequency)				
Passage	**Scheme #1**	**Scheme #2**	**Scheme #3**	**Scheme #4**	**Scheme #5**
1	T304I (12%)	T304I (12%)	T304I (12%)	T304I (12%)	none
2	T304I (15%)	T304I (45%)	T304I (45%)	T304I (45%)	T304I (5%)
3	T304I (38%)	T304I (79%)	T304I (79%)	T304I (79%)	T304I (77%)
4	T304I (66%)	T304I (83%)	T304I (81%)	T304I (81%)	T21I (31%), L50F (6%), T135I (7%), T304I (81%)
5	T304I (68%)	T304I (74%)	A173V (12%), T304I (74%)	A173V (12%), T304I (74%)	T21I (78%), L50F (6%), S144A (43%), A191V (5%), T304I (71%)
6	T304I (73%)	A173V (5%), T304I (75%)	A173V (93%), T304I (74%)	A173V (93%), T304I (74%)	T21I (99%), S144A (94%), T304I (73%)
7	T304I (75%)	A173V (93%), T304I (76%)	A173V (93%), T304I (77%)	A173V (89%), T304I (79%)	T21I (100%), S144A (95%), T304I (77%)
8	T304I (82%)	A173V (98%), T304I (80%)	L50F (21%), T135I (6%), A173V (98%), T304I (81%)	ND	T21I (100%), S144A (100%), T304I (83%)
9	T304I (80%)	A173V (97%), T304I (80%)	L50F (20%), A173V (98%), T304I (79%)	ND	T21I (100%), S144A (100%), T304I (81%)

Source: Adapted from (Pfizer 2022g), p. 30-31.
Abbreviations: M^{pro}, main protease; ND, no data, as viruses could not be recovered; NIR, nirmatrelvir; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

To determine whether the selected viruses had reduced susceptibility to NIR, the Applicant plaque-purified a total of 88 viruses from scheme #3, passage 7 and scheme #5, passages 4-5. The viruses were screened by Sanger sequencing to identify M^{pro} substitutions. Six viruses with different M^{pro} substitutions were selected for additional analysis. These viruses were further propagated in the absence and presence of NIR to produce virus stocks and prevent reversion of M^{pro} substitutions. The virus stocks were then sequenced by whole-genome Illumina sequencing to confirm the presence of the expected substitutions. NIR activity was then determined against the 6 viruses in Vero E6 P-gp knockout cells by nsp10 qRT-PCR assay. In most cases, the viruses further propagated in the presence of NIR were used for these experiments. However, the virus propagated in the absence of NIR was used for T304I.

The 6 viruses tested had M^{pro} T304I, T21I+T304I, L50F+T304I, T135I+T304I, A173V+T304I, or T21I+S144A+T304I substitutions (Table 227). For most viruses, the expected M^{pro} substitutions had frequencies ≥97%, but the L50F and T304I substitutions had frequencies of 49% and 80-82%, respectively. In response to an Information Request, the Applicant indicated that the T304I results may have been affected by a sequencing artifact. When sequencing was repeated with a different methodology, the T304I frequency in plaque-purified viruses was 99-100%. The Applicant did not comment on whether sequencing artifacts may have also been

responsible for the low frequency of L50F (49%) in plaque-purified virus. Relative to the parental virus (USA-WA1/2020, historical aggregate of 23 experiments), all 6 viruses had significantly reduced susceptibility to NIR. The virus with the T304I substitution alone had 3.4-fold reduced susceptibility to NIR (based on geometric mean EC_{50} value). The viruses with T21I + T304I, L50F + T304I, T135I + T304I, and A173V + T304I double substitutions had 3.8- to 20.2-fold reduced susceptibility to NIR, while the virus with the T21I + S144A + T304I triple substitution had 27.8-fold reduced susceptibility to NIR. All of the viruses remained fully susceptible to remdesivir. Overall, these results indicate that most of the M^{pro} substitutions contributed to NIR resistance, with the possible exception of T135I.

Table 227. Activity of NIR Against Plaque-Purified SARS-CoV-2 With M^{pro} Substitutions

	EC_{50} (nM)						EC_{90} (nM)				
M^{pro} Substitutions (Frequency)	n	GMean	95% CI Low Bound	95% CI High Bound	Fold-Change	p-value	GMean	95% CI Low Bound	95% CI High Bound	Fold-Change	p-value
none (control)	23	34.8	25.7	47.0	N/A	N/A	154	118	200	N/A	N/A
T304I (82%)	3	118	24.2	574	3.4	0.02	420	143	1,232	2.7	0.02
T21I (100%), T304I (81%)	3	275	136	554	7.9	<0.001	568	279	1,159	3.7	0.002
L50F (49%), T304I (80%)	4	205	72.4	582	5.9	<0.001	783	496	1,236	5.1	<0.001
T135I (100%), T304I (80%)	4	134	62.0	288	3.8	0.002	353	153	814	2.3	0.04
A173V (97%), T304I (82%)	3	702	150	3,287	20.2	<0.001	1,631	512	5,190	10.6	<0.001
T21I (100%), S144A (100%), T304I (82%)	4	967	438	2,136	27.8	<0.001	2,548	1,517	4,280	16.6	<0.001

Source: Adapted from (Pfizer 2022g), p. 35.
Note: P-values were determined by one-way ANOVA with Dunnett's post-test to compare EC_{50} values of each virus to the control virus (WA1/2020).
Abbreviations: CI, confidence interval; EC_{50}, half-maximal effective concentration; EC_{90}, 90% effective concentration; GMean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome 2

Of the 7 distinct M^{pro} substitutions observed (T21I, L50F, T135I, S144A, A173V, A191V, and T304I), 6/7 (all except T135I) have been associated with NIR resistance in cell culture by other groups, usually in combination with other M^{pro} substitutions (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023). In addition, the T21I + T304I, L50F + T304I, A173V + T304I, and T21I + S144A + T304I double or triple substitutions have all been associated with NIR resistance in other studies, although other M^{pro} substitutions were present as well in some cases. In biochemical assays (Section 20.1), the S144A and A173V substitutions significantly affected NIR activity (K_i fold-change ≥3), while the T21I, L50F, T135I, A191V, and T304I substitutions did not. Of the substitution combinations, the T135I + T304I, A173V + T304I, and T21I + S144A + T304I substitutions significantly affected NIR activity, while the T21I + T304I and L50F + T304I substitutions did not. Notably, the T304I substitution is located near the C-terminus of M^{pro}, which overlaps the nsp5/nsp6 M^{pro} cleavage site. T304I is located in the P3 position of the cleavage site and may affect binding of the nsp5/nsp6 cleavage site or M^{pro} autocleavage (Iketani et al. 2023). The finding that T304I did not affect NIR activity in biochemical assays (in which T304I was introduced into M^{pro} but not the peptide substrate) is

consistent with this hypothesis. M^{pro} substitutions at several other cleavage sites were also observed (not shown) but only sporadically and at low frequencies (3-6%).

These studies had several limitations. The findings were not confirmed with recombinant viruses. Replication kinetics in the absence of NIR were not determined. Alternative resistance pathways may have been missed, as a single virus stock was used to initiate the infections, and the first passage was shared for 4/5 passaging schemes. No data were provided regarding the structural or mechanistic basis of resistance.

Selection of NIR-Resistant SARS-CoV-2 in A549-ACE2 Cells (Pfizer 2022c)

The Applicant also selected NIR-resistant SARS-CoV-2 (USA-WA1/2020) in A549-ACE2 cells. The activity of NIR against SARS-CoV-2 WA1/2020 in A549-ACE2 cells was first determined by virus yield reduction assay. A549-ACE2 cells were infected in the presence of NIR for 2 days, followed by collection of supernatants and virus titration in Vero E6 cells by plaque assay. NIR had an EC_{50} value of ~50 nM in this assay. SARS-CoV-2 was serially passaged 7 times with NIR concentrations increasing from 300 nM ($6xEC_{50}$) to 2,500 nM ($50xEC_{50}$). These experiments were conducted using a single virus stock. Cells were infected at an MOI of 0.1 for passages 1-2, 0.01 for passage 3, and 0.001 for passages 4 to 7. Each passage lasted 3 to 6 days. After each passage, virus titers (pfu/mL) were determined by plaque assay in Vero E6 cells. In addition, viral RNA was extracted after each passage, and M^{pro} and M^{pro} cleavage site substitutions were identified by whole-genome Illumina sequencing.

After passage 3, an A173V M^{pro} substitution was detected at a high frequency (96%, Table 228). The A173V M^{pro} substitution remained predominant through passage 7, and no other major M^{pro} substitutions were detected. However, several M^{pro} substitutions were sporadically observed at low frequencies (3-9%), including I78F, K90R, S144A, and L205V. Virus titers were low after passages 6 to 7. The passaged viruses were also found to form smaller plaques in A549-ACE2 cells (in the absence of NIR), possibly indicating a replication defect. Thus, passage 6 and 7 viruses were plaque-purified and expanded in A549-ACE2 cells (in the absence of NIR), and 10 plaques were sequenced. The plaque-purified viruses were found to contain F140L + A173V M^{pro} substitutions. It is unclear why the F140L substitution was only detected in plaque-purified viruses.

Table 228. Sequencing of SARS-CoV-2 Passaged in the Presence of NIR in A549-ACE2 Cells

Passage	NIR (nM)	EC_{50} Multiples	Sample Description	M^{pro} Substitutions ≥50% (Frequency)
1	300	6×	Pooled Sample	none
2	300	6×	Pooled Sample	none
3	1,250	25×	Pooled Sample	A173V (96%)
4	1,250	25×	Pooled Sample	A173V (96%)
	2,000	40×	Pooled Sample	A173V (94%)
5	2,000	40×	Pooled Sample	A173V (93%)
	2,500	50×	Pooled Sample	A173V (88%)

Passage	NIR (nM)	EC_{50} Multiples	Sample Description	M^{pro} Substitutions ≥50% (Frequency)
6	2,000	40×	Pooled Sample	A173V (86%)
			Plaque-Purified	F140L (99%)+A173V (97%)
	2,500	50×	Pooled Sample	A173V (71%)
			Plaque-Purified	F140L (99%)+A173V (96%)
7	2,000	40×	Pooled Sample	A173V (85%)
			Plaque-Purified	F140L (98%)+A173V (96%)
	2,500	50×	Pooled Sample	A173V (65%)
			Plaque-Purified	F140L (99%)+A173V (98%)

Source: Adapted from (Pfizer 2022c), p. 17.
Abbreviations: EC_{50}, half-maximal effective concentration; M^{pro}, main protease; NIR, nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

The activity of NIR against two passaged viruses was determined in Vero E6-TMPRSS2 cells by nsp10 qRT-PCR assay. These experiments were performed in the presence of 2,000 nM CP-100356 (P-gp inhibitor). NIR inhibited replication of the parental virus (SARS-CoV-2 WA1/2020) with a geometric mean EC_{50} value of 61 nM (Table 229). NIR had similar activity against the P5 virus with the A173V substitution, indicating that the A173V substitution alone may not confer significant NIR resistance, as reported by others (Zhou et al. 2022b; Iketani et al. 2023). However, NIR had significantly reduced activity against the P7 virus with F140L+A173V substitutions, with a 10.1-fold higher EC_{50} value. This virus remained fully susceptible to remdesivir.

Table 229. Activity of NIR Against SARS-CoV-2 With M^{pro} Substitutions

Virus (M^{pro} Substitutions)	N	EC_{50} (nM) Geomean	EC_{50} (nM) Fold-Change	EC_{50} (nM) p-value	EC_{90} (nM) Geomean	EC_{90} (nM) Fold-Change	EC_{90} (nM) p-value
Control (none)	3	61	N/A	N/A	327	N/A	N/A
P5 (A173V)	3	57	0.9	0.88	130	0.4	0.006
P7 (F140L+A173V)	3	614	10.1	<0.001	1,308	4.0	<0.001

Source: Adapted from (Pfizer 2022c), p. 18.
Notes: P-values were determined by Dunnett t-test.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; Mpro, main protease; N/A, not applicable; NIR ,nirmatrelvir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Both the F140L and A173V M^{pro} substitutions have been associated with NIR resistance in cell culture by independent groups (Zhou et al. 2022b; Iketani et al. 2023). However, the F140L + A173V double substitution has not been observed by others. In biochemical assays (Section 20.1), the F140L, A173V, and F140L + A173V substitution led to 7.6-, 16-, and 95-fold higher K_i values, respectively, indicating that both substitutions contribute to resistance. These studies had several limitations. The findings were not confirmed with recombinant viruses. Replication kinetics in the absence of NIR were not determined. Alternative resistance pathways may have been missed, as a single virus stock was used to initiate the infections. No data were provided regarding the structural or mechanistic basis of resistance.

NIR Activity Against Recombinant SARS-CoV-2 Encoding M^{pro} Substitutions (Pfizer 2022l)

To determine the impact of M^{pro} substitutions on NIR activity in cell culture, the Applicant generated recombinant SARS-CoV-2 (WA1/2020-based) viruses using a previously described system (Xie et al. 2020a). The Applicant attempted to generate viruses with Mpro $G1^{5S,}$ Y54A,

E55L, E55L + S144A, L89F, K90R, F140A, S144A/E/L/P/T, H164N, E166A/V, H172Y, and Q189K substitutions. The E166V substitution was chosen because it was identified in several NIR-treated participants in trial EPIC-HR. The L89F and K90R substitutions were chosen because they represent naturally occurring polymorphisms that were not expected to affect NIR activity. The other substitutions were chosen because they significantly affected NIR activity in a biochemical assay and/or were identified in NIR-selected MHV. These substitutions were chosen prior to completion of the Applicant's studies on NIR-selected SARS-CoV-2 in cell culture and the publication of similar studies by independent groups. Only S144A, E166A/V, and H172Y have been associated with SARS-CoV-2 resistance to NIR in cell culture (Zhou et al. 2022b; Iketani et al. 2023; Jochmans et al. 2023).

The Applicant successfully generated 9/17 recombinant viruses with M^{pro} substitutions, while 8/17 viruses could not be generated because: 1. virus was not recovered, or 2. virus was recovered but did not encode the expected M^{pro} substitution (Table 230). In 2 cases (H164N and E166A), the initial virus recovered contained a mixture of sequences, but viruses encoding only the desired substitution were obtained by plaque purification. All virus stocks, whether produced by bulk passaging or plaque purification, were analyzed by Illumina sequencing to confirm the presence of only the desired substitutions.

The activity of NIR against recombinant SARS-CoV-2 viruses was tested in Vero E6 P-gp knockout cells by N qRT-PCR assay. Cells were infected at an MOI of 0.04 in the presence of NIR and incubated for 48 hr, followed by in-plate lysis and qRT-PCR. NIR inhibited the replication of WT SARS-CoV-2 (WA1/2020) with a mean EC_{50} value of 37 nM (Table 230). Of the 9/17 viruses successfully generated, only the virus with the E166A substitution had significantly reduced susceptibility to NIR, with an ~3.3-fold higher EC_{50} value. The virus with the S144A substitution had a 2.5-fold higher EC_{50} value, although the difference was not statistically significant. The S144A and E166A substitutions led to 46- and 35-fold reduced NIR activity in a biochemical assay (Table 211), respectively.

Table 230. Activity of NIR Against Recombinant SARS-CoV-2 With M^{pro} Substitutions

		EC_{50} (nM)			EC_{90} (nM)		
Virus	n	Mean	Fold-Change	p-Value	Mean	Fold-Change	p-value
WT	18	37	N/A	N/A	100	N/A	N/A
G15S	3	26	0.7	0.97	64	0.6	0.91
Y54A[a]	--	--	--	--	--	--	--
E55L	4	66	1.8	0.59	133	1.3	0.99
E55L+S144A[b]	--	--	--	--	--	--	--
L89F	3	48	1.3	1.00	212	2.1	0.41
K90R	3	56	1.5	0.94	113	1.1	1.00
F140Aa	--	--	--	--	--	--	--
S144A	4	94	2.5	0.08	195	1.9	0.41
S144E[a]	--	--	--	--	--	--	--
S144L[a]	--	--	--	--	--	--	--
S144P[a]	--	--	--	--	--	--	--
S144T[a]	--	--	--	--	--	--	--
H164N	3	71	1.9	0.58	158	1.6	0.91

		EC_{50} (nM)			EC_{90} (nM)		
Virus	n	Mean	Fold-Change	p-Value	Mean	Fold-Change	p-value
E166A	5	122	3.3	0.004	535	5.3	<0.001
E166V[a]	--	--	--	--	--	--	--
H172Y[a]	--	--	--	--	--	--	--
Q189K	4	8	0.2	<0.001	24	0.2	0.002

Source: Adapted from (Pfizer 2022l), p. 24.
Note: P-values were determined by Dunnett t-test.
[a.] No data (viruses could not be recovered)
[b.] Experiments in progress.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; M^{pro}, main protease; n, number of experiments; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WT, wild-type

In another report, NIR had a 2.2-fold higher EC_{50} value against recombinant SARS-CoV-2 with the M^{pro} S144A substitution, similar to the 2.5-fold change observed by the Applicant (Iketani et al. 2023). Thus, the S144A substitution alone confers only slightly reduced susceptibility to NIR. In two other reports, recombinant SARS-CoV-2 with the M^{pro} E166V substitution was successfully generated and found to have significantly reduced susceptibility to NIR, with 25-288-fold higher EC_{50} values (Zhou et al. 2022b; Iketani et al. 2023). The main limitation of the Applicant's study is that most of the M^{pro} substitutions (and combinations of substitutions) that were identified in NIR-selected SARS-CoV-2 (by the Applicant and others) have not yet been tested.

Other Studies Related to NIR Resistance in Cell Culture

- In Iketani et al., SARS-CoV-2 WA1/2020 was passaged in Vero E6 cells in the presence of NIR (Iketani et al. 2023). Three cultures were passaged. Culture #1 acquired 5 M^{pro} substitutions (T21I, C160F, A173V, V186A, T304I) and had 28.5-fold reduced susceptibility to NIR (based on EC_{50} value). Culture #2 acquired 4 M^{pro} substitutions (T21I, L50F, A193P, S301P) and had 28.8-fold reduced susceptibility to NIR. Culture #3 acquired 4 M^{pro} substitutions (L50F, F140L, L167F, T304I) and had 54.7-fold reduced susceptibility to NIR. SARS-CoV-2 was also passaged in Huh7-ACE2 cells in 480 wells, leading to the identification of 53 NIR-resistant cultures. Fourteen M^{pro} substitutions were identified in at least 2 cultures: T21I, L50F, P108S, S144A, E166A/V, T169I, H172Y, A173V, V186A, R188G, P252L, S301P, and T304I. Note that the S301P and T304I substitutions overlap the P6 and P3 positions, respectively, of the nsp5/nsp6 cleavage site.
- In Jochmans et al., (preprint), SARS-CoV-2 GHB-0302 was passaged in Vero E6 cells in the presence of the M^{pro} inhibitor ALG-097161 (Jochmans et al. 2023). The passaged virus acquired M^{pro} L50F, E166A, and L167F substitutions and was cross-resistant to NIR, with a 51-fold higher EC_{50} value. Recombinant SARS-CoV-2 (WA1/2020-based) with the L50F, E166A + L167F, and L50F + E166A + L167F substitutions had 1.5-, 10.0-, and 29-fold higher EC_{50} values, respectively, than WT virus.
- In Zhou et al., SARS-CoV-2 /DK-AHH1/2020 was passaged in Vero E6 cells in the presence of NIR or the HCV NS3/4A protease inhibitor boceprevir (Zhou et al. 2022b). Boceprevir is known to have activity against SARS-CoV-2 M^{pro} (Ma et al. 2020). Two viruses passaged in the presence of boceprevir were found to have reduced susceptibility to NIR (5-6-fold higher EC_{50} values): one with M^{pro} L50F, C160F, A173V, and A191V substitutions and one with M^{pro} L50F and A173V substitutions. Another virus passaged in the presence of NIR acquired

M^{pro} T21I and T304I substitutions and had 4-6-fold higher EC_{50} values. One additional virus passaged in the presence of NIR acquired M^{pro} L50F and E166V substitutions and had 78-175-fold higher EC_{50} values.

- Table 231 contains a list of all SARS-CoV-2 M^{pro} substitutions that were associated with NIR resistance in cell culture, either in the Applicant's studies or the studies described above. These substitutions were observed in numerous combinations. Refer to the cited studies for lists of all combinations that have been identified to date.

Table 231. SARS-CoV-2 M^{pro} Substitutions Associated With NIR Resistance in Cell Culture Across Different Studies

M^{pro} Substitution	Contact[1]	Biochemical Assay K_i Fold-Change	Applicant's Selection Studies	(Iketani et al. 2023)	(Jochmans et al. 2023)	(Zhou et al. 2022b)
T21I	No	1.6	X	X		X
L50F	No	0.2	X	X	X	X
P108S	No	2.9		X		
T135I	No	2.3	X			
F140L	Yes	7.6	X	X		
S144A	Yes	46	X	X		
C160F	No	0.6		X		X
E166A/V	Yes	35/7,700		X	X	X
L167F	Yes	<0.9		X	X	
T169I	No	<1.4		X		
H172Y	Yes	250		X		
A173V	No	16	X	X		X
V186A	Yes	<0.8		X		
R188G	Yes	38		X		
A191V	Yes	<0.8	X			X
A193P	No	0.9		X		
P252L	No	<0.9		X		
S301P[2]	No	0.2[e]		X		
T304I[2]	No	1.0[e]	X	X		X

Source: FDA analysis and pooled summary of Applicant's nonclinical virology/resistance reports and noted literature references.
[1] This column indicates residues in direct contact or close proximity (<5 Å) with NIR based on the Applicant's co-crystal structural analysis.
[2] Note that S301P and T304I overlap the P6 and P3 positions, respectively, of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}.
Note: Shading indicates substitutions that were observed in at least 2 studies.
Note: Biochemical data are from (Pfizer 2022h). For (Iketani et al. 2023), M^{pro} substitutions associated with NIR resistance in Huh7-ACE2 cells are only listed if they were observed in ≥2 cultures.
Abbreviations: K_i, inh bition constant; M^{pro}, main protease; ND, no data; NIR, nirmatrelvir; nsp, nonstructural protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

20.3.2. Cross-Resistance

Currently, NIR (in combination with ritonavir) is the only authorized M^{pro} inhibitor for the treatment of COVID-19. As described above, remdesivir retains activity against NIR-resistant SARS-CoV-2 in cell culture, as expected based on these products' distinct mechanisms of action. Similar findings have been reported by others (Zhou et al. 2022b; Iketani et al. 2023). The Applicant has not investigated the activity of NIR against SARS-CoV-2 viruses that are resistant to other antivirals approved or authorized by the FDA for COVID-19. However, NIR is expected to retain activity against such viruses due to its distinct mechanism of action. NIR is known to

exhibit partial cross-resistance with other SARS-CoV-2 M^{pro} inhibitors under development (Iketani et al. 2023).

20.3.3. Drug Resistance in Clinical Studies

Refer to Section 18: Clinical Virology.

20.4. Updated Nonclinical Virology/Resistance Data

Late in the review cycle, and after reviewing the data described in the sections above, the Applicant submitted the following nonclinical virology data on the activity of nirmatrelvir against additional SARS-CoV-2 Omicron sub-variants and phenotyping of M^{pro} substitutions using biochemical assays and recombinant viruses.

Nirmatrelvir Activity Against Additional SARS-CoV-2 Omicron Sub-Variants

In Report 042713 (v8), the Applicant determined the activity of NIR against SARS-CoV-2 USA-WA1/2020, BA.4.6, BF.7 (x2), BQ.1, BQ.1.11, and XBB.1.5 variants in Vero E6-TMPRSS2 cells by qRT-PCR, using the method described in Section 20.2.1 (Pfizer 2023c). NIR activity was tested in the presence of 2,000 nM CP-100356 (P-gp inhibitor). NIR retained activity against the
SARS-CoV-2 Omicron sub-variants BA.4.6, BF.7 (x2), BQ.1, BQ.1.11, and XBB.1.5, with fold-changes in geometric mean EC_{50} and EC_{90} values ≤1.5 relative to USA-WA1/2020 (Table 232).

Table 232. NIR Activity Against Additional SARS-CoV-2 Omicron Subvariants in Vero E6-TMPRSS2 Cells (With P-gp Inhibitor)

Variant	M^{pro} Polymorphism	n	Geomean EC_{50} (nM) (Range)	EC_{50} FC	Geomean EC_{90} (nM) (Range)	EC_{90} FC
USA-WA1/2020	N/A	30	99 (42-228)	N/A	218 (86-478)	N/A
Omicron BA.4.6	P132H	3	146 (116-200)	1.5	294 (239-414)	1.3
Omicron BF.7	P132H+T243I	4	76 (58-104)	0.8	157 (119-213)	0.7
Omicron BF.7	P132H+P252L+F294L	5	108 (59-190)	1.1	240 (174-397)	1.1
Omicron BQ.1	P132H	3	104 (79-126)	1.1	215 (158-266)	1.0
Omicron BQ.1.11	P132H	2[a]	90 (55-124)	0.9	190 (121-259)	0.9
Omicron XBB.1.5	P132H	6	113 (37-200)	1.1	228 (79-385)	1.0

Source: Adapted from (Pfizer 2023c), p. 19-20.
a. Mathematical average (n=2), not geomean.
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; FC, fold-change; Geomean, geometric mean; M^{pro}, main protease; n, number of experiments; N/A, not applicable; P-gp, P-glycoprotein; Polymorphs, polymorphisms; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Phenotypic Analysis of Additional M^{pro} Substitutions

In Report 121015 (v7), the Applicant determined the activity of NIR against recombinant SARS-CoV-2 M^{pro} enzymes with several additional substitutions in biochemical assays, using the method described in Section 20.1 (Pfizer 2023b). In total, 12 new enzymes were tested, which had
P108L, V186F, A193T/V, V202F/G/L, W207L, A260S/T, K269R, or T21I + C160F + A173V +

V186A + T304I substitutions. These substitutions were tested because they were: a) associated with PAXLOVID treatment in EPIC-HR, b) associated with nirmatrelvir resistance in cell culture, or c) were observed at nirmatrelvir contact or close proximity residues in the GISAID sequence database. Of these, only T21I + C160F + A173V + V186A + T304I significantly affected nirmatrelvir activity, with a 28-fold higher geometric mean K_i value compared to WT enzyme. The other substitutions did not significantly affect nirmatrelvir activity, with the following geometric mean K_i value fold-changes: P108L (0.3), V186F (0.5), A193T/V (0.5/0.4), V202F/G/L (0.6/0.4/0.3), W207L (0.7), A260S/T (0.3/0.5), and K269R (0.7).

In Report 024518 (v5), the Applicant determined the activity of NIR against recombinant SARS-CoV-2 viruses with several additional M^{pro} substitutions in Vero E6 P-gp knockout or Vero E6-TMPRSS2 cells (+2,000 nM CP-100356, P-gp inhibitor), using the method described in Section 20.3.1 (Pfizer 2023d). The Applicant attempted to generate 14 viruses, which had M^{pro} F140I/L/S, S144A, E166G, A173S/T, A191V, Q192L, T304I, E55L + S144A, S144A + T304I, E166G + L232I, and T21I + A260V + T304I substitutions. Of these, 4/14 viruses (F140I/S, A173T, and A191V) could not be generated because the virus could not be recovered or lacked the desired substitutions. Of the 10/14 viruses successfully recovered, 6/10 had significantly reduced susceptibility to NIR, with the following mean EC_{50} value fold-changes relative to WA1-2020: F140L (4.1), S144A (5.3), A173S (3.2), E55L + S144A (6.5), S144A + T304I (3.1), and T21I + A260V+T304I (3.2). NIR retained activity (EC_{50} value fold-change <3) against the other 4/10 viruses, with the following mean EC_{50} value fold-changes: E166G (1.1), Q192L (1.2), T304I (1.4), and E166G+L232I (2.9).

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Reference ID: 5179402

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section 6.3.1.

23. Labeling: Key Changes and Considerations

Prescribing Information

Prescribing Information Labeling Review

Applicant's proposed labeling submitted on June 29, 2022, was compared with final agreed upon labeling. This review summarizes the major label changes and provides a cross reference to other sections of the Integrated Review for additional details and rationale for the labeling changes. Edits to highlights and table of contents were made to capture changes to the full prescribing information.

General Changes to Prescribing Information

BOXED WARNING

The following Boxed Warning to alert healthcare providers of the significant drug interactions with PAXLOVID was added. See Section 7.7.1 for additional detail.

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].***

1 INDICATIONS AND USAGE

Indications statement was modified [redacted] (b) (4) See Section 8.3 for additional detail.

Limitations of Use: Removed the LOU [redacted] (b) (4) See Section 6.3.5 for additional detail.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

Included additional description of the two different dose packs available for PAXLOVID to avoid potential medication error.

[redacted] (b) (4)

4 CONTRAINIDCATIONS

Added the following under the drug interaction contraindication to alert healthcare providers of important qualifications related to list of contraindicated drugs listed in this section: There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor [redacted] (b) (4) *[see Drug Interactions (7.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

- Highlighted [redacted] (b) (4), life-threatening, and/or fatal adverse reaction due to drug interactions with calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.
- Provided risk mitigation steps to healthcare provider to avoid potentially significant drug interactions including review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.
- Added benefit risk statement of considering the benefit of PAXLOVID versus risk of potential DDI.

5.2 Hypersensitivity Reactions

- Added serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome (SJS)). See Section 7.6.3.3 for additional detail.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- [redacted] was removed. See Section 7.6.2 for additional detail. Added safety data from EPIC-SR (vaccinated or unvaccinated subjects at standard risk of fully vaccinated subjects with at least 1 risk factor for progression to severe disease).
- Moved adverse reactions reported under EUA [redacted] to subsection 6.1 Clinical Trials Experience and added the following additional events: anaphylaxis, Toxic Epidermal Necrolysis, Stevens-Johnsons syndrome, headache, hypertension, and vomiting.

7 DRUG INTERACTIONS

7.3 Established and Other Potentially Significant Drug Interactions

Added the following additional drug interactions to Table 1. Established and Other Potentially Significant Drug Interactions: tamsulosin, apixaban, primidone, clonazepam, rifapentine, silodosin, eplerenone, ivabradine, aliskiren, ticagrelor, vorapaxar, clopidogrel, cilostazol, lumacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, saxagliptin, voclosporin, everolimus, tofacitinib, upadacitinib, lomitapide, eletriptan, ubrogepant, Rimegepant, finerenone, darifenacin, hydrocodone, oxycodone, meperidine, suvorexant, aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin, naloxegol, tadalafil, riociguat, avanafil, vardenafil, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, tolvaptan with appropriate clinical comments.

Most of these additions mirrored additions to the EUA Fact Sheet for Healthcare Providers during the course of the NDA review (please see the EUA review memos for more details).

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

[redacted] has been removed and replaced with the following statement: The optimal dose of PAXLOVID has not been established in pediatric patients.

8.5 Geriatric Use

The following statement was added: No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Changed mechanism of action (MoA) to nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug. Additional details moved to Section 12.4 for consistency with other antiviral drug labels.

12.2 Pharmacodynamics

Removed [redacted], and a high-level summary of clinical antiviral activity was added to Section 12.4 Microbiology.

12.3 Pharmacokinetics

[redacted] The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3 of the USPI. Additional PK parameters from healthy subjects were added to Table 2 of the USPI including food effect and the percentage of dose excreted as total (unchanged drug) in feces and urine.

12.4 Microbiology

Section was modified and expanded to describe MoA (details moved from 12.1, see above), add updated data on nirmatrelvir antiviral activity against different SARS-CoV-2 variants, add high level summary of clinical antiviral activity [redacted], remove [redacted] re-organized and included additional details on potential resistance-associated substitutions, describe resistance-associated substitutions detected in subjects with viral RNA rebound, and include a brief summary of analyses of symptom rebound. See Sections 18 and 20 for additional detail.

[redacted]

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk for Progressing to Severe COVID-19

- Included COVID-19 related hospitalization through Day 28 in Table 8 USPI, the efficacy table for EPIC-HR.
- Added secondary endpoint of all-cause mortality through Week 24 for PAXLOVID and placebo in footnote of Table 8 of USPI.
- Added data on COVID-19 related hospitalization or death from any cause through Day 28, with confidence interval, in subjects who were SARS-CoV-2 seropositive at baseline.
- See Section 6.2.1.4 for additional detail.

14.2 [redacted] Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19

- Removed [redacted] and included statement that primary endpoint of the trial was the difference in time to sustained alleviation of all

targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients was not met.

- Added the following: In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.
- See Section 6.2.2.4 for additional detail.

14.3 Post-Exposure Prophylaxis

Removed [redacted] (b) (4) and included the following: The primary endpoint for this trial was not met. PAXLOVID is not indicated for post-exposure prophylaxis of COVID-19. See Section 6.2.3.4 for additional detail.

Packaging

The proposed packaging of the PAXLOVID commercial product, including the carton labeling and container labels, was reviewed for areas of vulnerability that may lead to medication errors. The final packaging incorporated Agency recommendations to maximize safe use. Differences between the commercial packaging and the PAXLOVID packaging under EUA include the following:

- Each carton will contain ten single dose blister cards, rather than five blister cards containing both the morning and the evening dose.
- Bolding, font size, and language were adjusted and arrows were added to the container labels to further clarify dosing instructions.
- The size, color, language, and placement of language on the carton labeling were adjusted to further distinguish the dose pack for patients with moderate renal impairment from the dose pack for patients with normal renal function or mild renal impairment.
- The carton labeling was revised to include the following alert to patients: “Find out about medicines that should not be taken with Paxlovid.”

For further details, please refer to the Office of Surveillance and Epidemiology (OSE) Label and Labeling Reviews by Melina Fanari, Madhuri Patel, and Mishale Mistry from September 1 and December 12, 2022, and the OSE Reviews of Revised Label and Labeling by Melina Fanari and Madhuri Patel from January 9 and May 2, 2023 (DARRTS ID: 5077785 2022).[20]

[20] The referenced documents contain proprietary data obtained by FDA and cannot be released to the public. The information contained within is the result of an OSE review as part of PAXLOVID, NDA 217188. The source documents can only be accessed by authorized individuals.

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- USPI
- Patient package insert (PPI)
- Carton and container labeling

24. Postmarketing Requirements and Commitments

24.1. Postmarketing Requirements

The following postmarketing requirements (PMRs) will be issued at the time of approval (note that wording changes may occur between those listed below and in the approval letter):

24.1.1. Pediatric Research Equity Act PMR 4392-1

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 6 to less than 18 years of age and weighing 20 kg or higher, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.2. Pediatric Research Equity Act PMR 4392-2

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects 2 to less than 6 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.3. Pediatric Research Equity Act PMR 4392-3

Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of PAXLOVID in pediatric subjects from birth to less than 2 years of age, with mild-to-moderate coronavirus disease 2019 (COVID-19).

24.1.4. PMR 4392-4

Conduct studies to characterize the phenotypic effects of the following amino acid substitutions on nirmatrelvir anti-SARS-CoV-2 activity: M^{pro} substitutions G11V, L30I, T45N, A94V, T98I/R/del, V104I, W207/R/del, F223L, H246Y; M^{pro} cleavage site substitutions A3571V, V3855I, A5328S/V, S6799A. M^{pro} substitutions can be evaluated in biochemical assays using recombinant M^{pro} proteins or cell culture assays using recombinant SARS-CoV-2 viruses or replicons. The M^{pro} cleavage site substitutions should be evaluated in cell culture assays using recombinant SARS-CoV-2 viruses or replicons.

24.1.5. PMR 4392-5

Conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Conduct surveillance activities on at least a monthly basis. Conduct phenotypic analysis for any M^{pro} or M^{pro} cleavage site polymorphisms that are detected at a frequency ≥1% either globally or in the U.S. for any single month. These surveillance activities should continue for a period of 3 years post-approval, with re-assessment of the duration, frequency of reporting and additional protocol methods to occur on an annual basis.

24.1.6. PMR 4392-6

Submit the final report with datasets for the ongoing trial, "A Phase 1, Open-Label, Non-Randomized Study To Investigate The Safety And PK Following Multiple Oral Doses Of PF-07321332 (Nirmatrelvir)/Ritonavir In Adult Participants With COVID-19 And Severe Renal Impairment Either On Hemodialysis Or Not On Hemodialysis" (Study C4671028; NCT05487040).

24.2. Postmarketing Commitments

The following postmarketing commitments (PMCs) will be issued at time of approval (note that wording changes may occur between those listed below and in the approval letter):

24.2.1. PMC 4392-7

Submit the final study report with datasets for the ongoing trial, "An Interventional Efficacy And Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study To Investigate Nirmatrelvir/Ritonavir In Nonhospitalized Participants At Least 12 Years Of Age With Symptomatic COVID-19 Who Are Immunocompromised" (Study C4671034; NCT05438602).

24.2.2. PMC 4392-8

Submit the final study report with datasets for the ongoing trial, "A Phase 1, Open-Label Study To Evaluate The Pharmacokinetics, Safety, And Tolerability Of Orally Administered Nirmatrelvir/Ritonavir In Pregnant Women With Mild-To-Moderate COVID-19" (Study C4671035; NCT05386472).

24.2.3. PMC 4392-9

Submit the final study report with datasets for the ongoing trial, "A Phase I, Multiple Dose, Open-Label Pharmacokinetic Study Of Nirmatrelvir/Ritonavir In Healthy Lactating Women" (Study C4671039; NCT05441215).

24.2.4. PMC 4392-10

Conduct an observational study to evaluate pregnancy and infant outcomes following exposure to PAXLOVID during pregnancy.

24.2.5. PMC 4392-11

Submit the final study report with datasets for the ongoing trial, "An Interventional, Efficacy And Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study To Investigate A Repeat 5-Day Course Of Nirmatrelvir/Ritonavir Compared To Placebo/Ritonavir In Participants At Least 12 Years Of Age With Rebound Of COVID-19 Symptoms And Rapid Antigen Test Positivity" (Study C4671042; NCT05567952).

24.2.6. PMC 4392-12

Conduct a study to evaluate the activity of nirmatrelvir (±ritonavir) in combination with remdesivir against SARS-CoV-2 in cell culture.

24.2.7. PMC 4392-13

Conduct a study using cell culture assays to characterize the effect of nirmatrelvir/ritonavir on the anti-influenza virus activity of (a) oseltamivir and (b) baloxavir, and conversely the effect of (a) oseltamivir and (b) baloxavir on the anti-SARS-CoV-2 activity of nirmatrelvir/ritonavir

24.2.8. PMC 4392-14

Complete the proposed ecotoxicity studies that are currently in progress and update the environmental analysis report.

24.2.9. PMC 4392-15

Submit three-month long-term and accelerated stability data for three batches of nirmatrelvir tablets manufactured at the (b) (4)

25. Financial Disclosure

Table 241. Covered Clinical Studies: C4671002,C4671005, C4671006, C4671008, C4671010, C4671011, C4671012, C4671013, C4671014, C4671015, C4671019

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1955		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 26		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: CFR, Code of Federal Regulations; FDA, Food and Drug Administration

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26.2. Reports

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26.4. Guidances

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27. Review Team

Table 242. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Myung-Joo Patricia Hong, MS
Nonclinical reviewer	Zheng “Jenny” Li, PhD, DABT
Nonclinical team leader	Chris Ellis, PhD
OCP reviewer(s)	Cristina Miglis, PharmD, MS Ye Xiong, PhD
OCP team leader(s)	Mario Sampson, PharmD Jiang Liu, PhD Ying-Hong Wang, PhD Manuela Grimstein, PhD
Clinical reviewers	Glen Huang, DO Stephanie Troy, MD
Clinical team leader	Sarah Connelly, MD
Clinical Virology reviewers	Patrick Harrington, PhD Jonathan Rawson, PhD
Clinical Virology TL	Jules O’Rear, PhD
Biometrics reviewer	Jie Cong, PhD
Supervisory Mathematical Statistician (DBIV), Biometrics Secondary Reviewer	Thamban Valappil, PhD
Cross-disciplinary team leader	Sarah Connelly, MD
Division director (pharm/tox)	Hanan Ghantous, PhD, DABT
Associate Director for Labeling	Stacey Min, PharmD
Associate Director for Therapeutic Review (OCP)	Vikram Arya, PhD, FCP
Supervisory Mathematical Statistician (DBIV), Biometrics Tertiary Reviewer	Scott Komo, DrPH
Division director (clinical)	Debra Birnkrant, MD
Office director (or designated signatory authority)	John Farley, MD

Abbreviations: DBIV, Division of Biometrics IV; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; TL, team lead

Table 243. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
RBPM	Erica Keafer, MS Musse Olani, PharmD
Drug Substance	Katherine Windsor, PhD Paresma Patel, PhD (TL)
Drug Product	Shalini Anand, PhD David Claffey, PhD
Process/Facility/Microbiology (OPMA)	Abdollah Koolivand, PhD Hang Guo, MS (TL)
Biopharmaceutics	Gerlie Gieser, PhD Elsbeth Chikhale, PhD (TL)
Environment Assessment	Xiaoqin Wu, PhD Janes Laurenson, PhD
CMC ATL	David Claffey, PhD
OPDP	Wendy Lubarsky, PharmD Sam Skariah, PharmD
OSI	Elena Boley, MD, MBA Phillip Kronstein, MD (TL)
DMPP	Susan Redwood, MPH, BSN, RN Barbara Fuller, PharmD (TL)
OSE/DMEPA	Melina Fanari, PharmD Madhuri Patel, PharmD (TL) Mishale Mistry, PharmD, MPH, Associate Director
OSE/OPE/DPV II	Kate McCartan, MD Rachna Kapoor, PharmD, MBA (TL)
OSE/OPE/DEPI II	Natasha Pratt, PhD John Rhee, PharmD, MS Sheheryar Muhammad, PharmD (TL)
OB/DB VII	Jiwei He, PhD Yong Ma, PhD (TL)
Other	
Medical Editor	Noah Benjamin Whiteman, BA Mei Lu Joseph Dorn, MPH (TL)
Clinical Data Scientist	Jun Zhu, PhD Jinzhong Liu, MD (TL)
CluePoints Analyst	Xiaofeng Wang, MS Paul Schuette, PhD (TL)
AC Designated Federal Officer	Joyce Frimpong, PharmD Yvette Waples, PharmD (TL)

Abbreviations: AC, advisory committee; ATL, Application Team Lead; CMC, chemistry, manufacturing, and controls; DB VII, Division of Biometrics VII; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRISK, Division of Risk Management; OB, Office of Biostatistics; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, regulatory business process manager; TL, team lead

27.1. Reviewer Signatures

See next page.

Reference ID: 5179402

Table 244. Signatures of Reviewers

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Reviewer	Stephanie Troy Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 2.1, 2.2, 3.1, 6.3.1, 6.3.2, 6.3.4, 6.3.5, 6.3.7, 7.7, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Stephanie B. Troy -S Digitally signed by Stephanie B. Troy -S Date: 2023.05.22 10:22:42 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Reviewer	Glen Huang Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:.3, 4, 7.2, 7.3, 7.4, 7.5, 7.6, 8.3, 8.4, 17, 21, 22, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Glen Huang -S Digitally signed by Glen Huang -S Date: 2023.05.22 10:25:05 -04'00'					
Clinical Virology Reviewer	Patrick Harrington Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6, 18	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Patrick Harrington -S Digitally signed by Patrick Harrington -S Date: 2023.05.22 10:30:43 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Virology Reviewer	Jonathan Rawson Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 6, 18, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jonathan M. Rawson -S Digitally signed by Jonathan M. Rawson -S Date: 2023.05.22 10:39:41 -04'00'					
Clinical Virology Team Leader	Jules O'Rear Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 6, 18, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Julian J. O'rear -S Digitally signed by Julian J. O'rear -S Date: 2023.05.22 10:44:07 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Pharmacology/ Toxicology Reviewer	Jenny Li Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Zheng Li -S Digitally signed by Zheng Li -S Date: 2023.05.22 11:56:54 -04'00'					
Pharmacology/ Toxicology Team Leader	Christopher Ellis Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Christopher E. Ellis -S Digitally signed by Christopher E. Ellis -S Date: 2023.05.22 11:52:25 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Associate Director for Labeling	Stacey Min Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Stacey Min -S Digitally signed by Stacey Min -S Date: 2023.05.22 09:12:23 -04'00'					
Clinical Pharmacology Reviewer	Cristina Miglis Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Cristina M. Miglis -S Digitally signed by Cristina M. Miglis -S Date: 2023.05.22 09:07:43 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Secondary Reviewer	Mario Sampson Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Mario Sampson -S Digitally signed by Mario Sampson -S Date: 2023.05.22 08:37:55 -05'00'					
Clinical Pharmacology Reviewer	Ye Xiong Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2, 14.5.3, 14.5.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2023.05.22 09:54:39 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Jiang Liu Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2, 14.5.3, 14.5.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.05.22 19:22:26 -04'00'					
Clinical Pharmacology Team Leader	Yuching Yang Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.5.1, 14.5.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2023.05.22 10:29:01 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Team Leader	Manuela Grimstein Office of Clinical Pharmacology DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2023.05.22 11:14:25 -04'00'					
Clinical Pharmacology/ Pharmacometrics Primary Reviewer	Ying-Hong Wang Office of Clinical Pharmacology/ DPM	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒Yes ☐ No
Signature/date/time stamp: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2023.05.22 11:22:27 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Clinical Pharmacology Tertiary Reviewer	Vikram Arya Office of Clinical Pharmacology DIDP	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Vikram Arya -S Digitally signed by Vikram Arya -S Date: 2023.05.22 08:21:51 -04'00'					
Biometrics Primary Reviewer	Jie Cong Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jie Cong -S Digitally signed by Jie Cong -S Date: 2023.05.22 10:38:58 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Secondary Reviewer	Thamban Valappil Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S Date: 2023.05.22 10:44:32 -04'00'					
Biometrics Tertiary Reviewer	Scott Komo Office of Biostatistics DB IV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 3.2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Scott S. Komo -S Digitally signed by Scott S. Komo -S Date: 2023.05.22 10:53:26 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Biometrics Primary Reviewer	Jiwei He Office of Biostatistics DB VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 16.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Jiwei He -S Digitally signed by Jiwei He -S Date: 2023.05.22 11:38:57 -04'00'					
Biometrics Team Leader	Yong Ma Office of Biostatistics DB VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 16.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Yong Ma -S Digitally signed by Yong Ma -S Date: 2023.05.22 11:55:00 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Primary Reviewer	Natasha Pratt Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 7.7, 16.5, 21	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Natasha C. Pratt -S Digitally signed by Natasha C. Pratt -S Date: 2023.05.22 10:48:03 -04'00'					
Other Primary Reviewer	John Rhee Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: John T. Rhee -S Digitally signed by John T. Rhee -S Date: 2023.05.22 11:25:44 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Team Leader	Sheheryar Muhammad Office of Surveillance and Epidemiology Division of Epidemiology II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sheheryar Muhammad -S Digitally signed by Sheheryar Muhammad -S Date: 2023.05.22 11:29:23 -04'00'					
Other Reviewer	Kate McCartan Office of Surveillance and Epidemiology DPV II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Kate L. Mccartan -S Digitally signed by Kate L. Mccartan -S Date: 2023.05.22 12:14:47 -04'00'					

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Team Leader	Rachna Kapoor Office of Surveillance and Epidemiology DPV II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Rachna Kapoor -S Digitally signed by Rachna Kapoor -S Date: 2023.05.22 12:21:28 -04'00'					
Product Quality Supervisor	David Claffey Office of Pharmaceutical Quality ONDP/DNDP1	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: David J. Claffey -S Digitally signed by David J. Claffey -S Date: 2023.05.22 13:44:05 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Cross-Disciplinary Cross-Disciplinary Team Lead	Sarah Connelly Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Sarah M. Connelly -S Digitally signed by Sarah M. Connelly -S Date: 2023.05.22 09:47:39 -04'00'					
Regulatory Project Management Regulatory Project Manager	Myung-Joo P. Hong Other DROID	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Myung-joo P. Hong -S Digitally signed by Myung-joo P. Hong -S Date: 2023.05.23 10:16:40 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Deputy Director (Safety)	Poonam Mishra Office of Infectious Diseases DAV	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Poonam Mishra -S Digitally signed by Poonam Mishra -S Date: 2023.05.23 02:21:36 -04'00'					
Other Division Director	Hanan Ghantous Office of Infectious Diseases DPT-ID	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No
Signature/date/time stamp: Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S Date: 2023.05.22 11:56:12 -04'00'					

Reference ID: 5179402

Discipline and Role	Reviewer, Office, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory	Consent To Include on Public List of Reviewers
Other Division Director	Debra Birnkrant Office of Infectious Diseases DAV	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.		☒ Yes ☐ No

Signature/date/time stamp:

Debra B. Birnkrant -S

Digitally signed by Debra B. Birnkrant -S
Date: 2023.05.22 11:27:11 -04'00'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH M CONNELLY
05/24/2023 03:04:49 PM

DEBRA B BIRNKRANT
05/24/2023 03:06:51 PM

JOHN J FARLEY
05/24/2023 04:25:23 PM