

Emergency Use Authorization (EUA) for PAXLOVID

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000105
Date of Memorandum	June 28, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	<p>Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755 Karen Baker- Director Global Regulatory Affairs – Brand Hospital Products Email: (b) (6) Phone: (b) (6)</p>
Original Authorization	December 22, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	PAXLOVID
Established Name/Other names used during development	Nirmatrelvir (PF-07321332) tablets; Ritonavir tablets
Dosage Forms/Strengths	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days.
Therapeutic Class	<p><u>Nirmatrelvir</u> is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor that has demonstrated activity against SARS-CoV-2.</p> <p><u>Ritonavir</u> is an HIV-1 protease inhibitor and is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.</p>
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Rationale for Revisions to EUA Fact Sheets and Other Documents

The PAXLOVID EUA Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents, and Caregivers; and Patient Eligibility Screening Checklist Tool for Prescribers are being revised at this time for the following reasons:

1. To update the Fact Sheet for Healthcare Providers and the Patient Fact Sheet with post-authorization reports of abdominal pain, nausea, and malaise.

Since the original PAXLOVID EUA in December 2021, post-authorization reports have suggested the adverse events (AEs) of abdominal pain, nausea, and malaise may be associated with PAXLOVID use.

- Abdominal Pain
 - Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that abdominal pain was associated with PAXLOVID use, with similar low rates reported among PAXLOVID and placebo recipients ($\leq 1\%$ of each group when pooling related terms). From the January 5, 2022, clinical study report for EPIC-HR, the following was reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively, for AEs with preferred terms (PTs) that could be categorized as abdominal pain:
 - abdominal pain PT: 2 (0.2%) versus 3 (0.3%) subjects
 - abdominal pain lower PT: 1 (0.1%) versus 0 subjects
 - abdominal pain upper PT: 3 (0.3%) versus 2 (0.2%) subjects
 - dyspepsia PT: 6 (0.5%) versus 5 (0.4%) subjects
 - Post-Authorization Cases: The Sponsor identified a total of 38 cases of abdominal pain with PAXLOVID use from their global safety database, of which 12 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, the Office of Surveillance and Epidemiology's Division of Pharmacovigilance (DPV) noted that abdominal pain was among the most commonly reported unlabeled adverse events with PAXLOVID use identified in the FDA Adverse Event Reporting System (FAERS).
 - Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), abdominal pain is included among the most frequently reported adverse drug reactions, with a reported frequency of 26%.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020659s072,022417s024,209512s007lbl.pdf).
- Nausea

- Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that nausea was associated with PAXLOVID use, with similar low rates reported among PAXLOVID and placebo recipients. From the January 5, 2022, clinical study report for EPIC-HR, the following was reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively:
 - Nausea PT: 16 (1.4%) versus 19 (1.7%)
 - Vomiting PT: 12 (1.1%) versus 9 (0.8%)
- Post-Authorization Cases: The Sponsor identified a total of 56 cases of nausea with PAXLOVID use from their global safety database, of which 23 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, DPV noted that nausea was among the most commonly reported unlabeled adverse events with PAXLOVID use identified in FAERS.
- Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), nausea and vomiting are each included among the most frequently reported adverse drug reactions, with reported frequencies of 57% and 32%, respectively.
- Malaise
 - Clinical trial data: There was no clear signal from EPIC HR, the clinical trial on which the initial authorization was based, that malaise was associated with PAXLOVID use. From the January 5, 2022, clinical study report for EPIC-HR, the following rates were reported among the **1109** PAXLOVID recipients versus the **1115** placebo recipients, respectively, for AEs with PTs similar to malaise (malaise specifically was not reported):
 - Asthenia PT: 3 (0.3%) versus 3 (0.3%)
 - Fatigue PT: 2 (0.2%) versus 5 (0.4%)
 - Post-Authorization Cases: The Sponsor identified a total of 67 cases of malaise with PAXLOVID use from their global safety database, of which 29 were assessed by the Sponsor as having a reasonable possibility of a causal association based on a temporal relationship and lack of significant confounding factors. In addition, DPV noted that malaise and feeling abnormal were among the most commonly reported unlabeled adverse events with PAXLOVID use identified in FAERS.
 - Norvir Labeling: In the label for Norvir (ritonavir administered as a dose of 600 mg po bid), fatigue/asthenia is included among the most frequently reported adverse drug reactions, with a reported frequency of 46%.

The Sponsor proposed adding abdominal pain, nausea, and malaise to the Fact Sheet for Healthcare Providers under Section 6.2, Post-Authorization Experience, as well as to the other possible side effects in the PAXLOVID Fact

Sheet for Patients, Parents, and Caregivers. Based on the post-authorization cases listed above combined with the frequent adverse drug reactions included in Norvir labeling, we agree with these additions.

2. To update the drug-drug interaction information in the Fact Sheet for Healthcare Providers and the Patient Fact Sheet.

The original listing of drugs either contraindicated with PAXLOVID or with other clinically significant drug interactions with PAXLOVID was compiled by the Sponsor based on the NORVIR (ritonavir) US package insert, NORVIR 100 mg summary of product characteristics (SmPC), and KALETRA (lopinavir/ritonavir) US package insert. NORVIR was first approved in 1996, and Section 7.1 in the NORVIR label contains the following caveat about the listing of drugs that interact with ritonavir: “These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with ritonavir. The healthcare provider should consult appropriate references for comprehensive information.” A similar caveat is included in the PAXLOVID Fact Sheet for Healthcare Providers; the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers; and the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers.

However, some of the drugs that may interact with PAXLOVID, and which are not listed in the Fact Sheet for Healthcare Providers, may lead to serious adverse drug reactions. For example, a safety brief published by the Institute for Safe Medication Practices in May described a case of fatigue and bradycardia, with a heart rate below 40 beats per minute, that required evaluation and treatment in the emergency department, in a patient who was taking ivabradine and was prescribed PAXLOVID for COVID-19. Ivabradine is contraindicated with strong CYP3A inhibitors in the ivabradine prescribing information because strong CYP3A inhibitors increase ivabradine plasma concentrations and may exacerbate bradycardia and conduction disturbances; however, a potential drug interaction with ivabradine is not included in the NORVIR prescribing information nor the PAXLOVID fact sheets or checklist tool. Furthermore, PAXLOVID is more widely prescribed than NORVIR; NORVIR has been prescribed predominantly by HIV providers experienced with ritonavir drug interactions, which may not be the case for PAXLOVID. Finally, as the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers was developed as a resource for prescribers to help navigate what they should be checking when prescribing PAXLOVID and to minimize confusion about what is required under EUA, prescribers may not be aware, even with the caveat about the list not being comprehensive, that serious adverse drug reactions could occur due to interactions with drugs not included on the listing.

Consequently, additional drugs are being added to the Fact Sheet for Healthcare Providers listing of contraindicated drugs in Section 4 and the listing of drugs with established and other potentially significant drug interactions in Table 1 in Section 7.3; these drugs either have listed drug reactions with strong CYP3A inhibitors in their prescribing information, are strong CYP3A inducers, are included as having drug interactions with ritonavir in the labeling of other ritonavir-containing products or in NORVIR labeling, or present a significant safety risk if omitted. For example, primidone, the label for which has not been updated to include pertinent drug-drug interaction data, was added to the list of contraindicated medications. The review team included this interaction in the fact sheet since 1) primidone is metabolized by CYP3A4 to the active metabolite phenobarbital, which is contraindicated with PAXLOVID and 2) primidone is included with phenobarbital as an example of a moderate clinical inducer for P450-mediated metabolisms for concomitant use clinical DDI studies and/or drug labeling. In addition, caveat language about the listed drugs being a guide and not a comprehensive list, that was already included in Section 7.3, is also being added to Sections 2.4 (Important Drug Interactions with PAXLOVID), 4 (CONTRAINDICATIONS), and 5.1 (Risk of Serious Adverse Reactions Due to Drug Interactions) for intentional redundancy to emphasize this point. Further additions to the listing of drugs either contraindicated with PAXLOVID or with other clinically significant drug interactions with PAXLOVID may be made in future EUA revisions; the drugs being added with this revision are listed below:

- Drugs being added to Section 4 (CONTRAINDICATIONS) and Table 1 in the Fact Sheet for HealthCare Providers; the list under “Do not take PAXLOVID if you are taking any of the following medicines” in the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers; and as medications with a red interaction code (contraindicated medications) in the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers:
 - Silodisin, eplerenone, ivabradine, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primodine, and lumacaftor/ivacaftor
- Drugs being added to Table 1 in the Fact Sheet for Healthcare Providers and as medications with a yellow interaction code (coadministration with PAXLOVID should be avoided and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary) in the PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers:
 - Tamsulosin, rifapentine, 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).

Section 7 (Drug Interactions) of the Fact Sheet for Healthcare Providers is also being revised for the following reasons:

- The text in Section 7.1 is being revised to emphasize that ritonavir is a strong CYP3A inhibitor. The text in Section 7.3 describing Table 1 is being revised to provide a suggestion for other resources that can be used to find comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor. Section 7.3 already included a statement that the drugs listed were a guide and not a comprehensive list of all possible drugs that may interact with PAXLOVID.
- Propoxyphene is being removed from Table 1 and from the list of contraindicated drugs in Section 4 (as well as from the list of contraindicated drugs in the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers) because it is no longer available in the United States.
- Bepridil is being removed from Table 1 because it is no longer available in the United States.
- For the anticonvulsants, the effect of PAXLOVID on the concentration of the anticonvulsants was removed as the reason for the contraindication is the effect of the anticonvulsants on the PAXLOVID concentration.
- The lists of anti-HIV protease inhibitors and other anti-HIV drugs are being streamlined to retain the commonly used antiretrovirals and to remove the antiretrovirals that are either no longer marketed or rarely prescribed in the United States. In addition, raltegravir is being removed for consistency with the raltegravir label, which lists other ritonavir-containing products (atazanavir/ritonavir, darunavir/ritonavir, and tipranavir/ritonavir) among the drugs without clinically significant interactions with raltegravir. Finally, the Effect on Concentration column for the Anti-HIV drug class was edited to include a concentration effect of PAXLOVID on nevirapine (↑ nevirapine), given nevirapine is extensively metabolized by CYP3A.
- The clinical comments related to the immunosuppressants (cyclosporine, tacrolimus, sirolimus, and now everolimus) in Table 1 are being revised to emphasize that use of PAXLOVID should be avoided when close monitoring of immunosuppressant concentrations is not feasible and to add language about monitoring for immunosuppressant-associated adverse reactions, immunosuppressant dose reduction, and obtaining expert consultation from the patient's immunosuppressive therapy specialist. The clinical comments already stated that therapeutic concentration monitoring is recommended, that PAXLOVID use should be avoided when close monitoring of immunosuppressant serum concentrations is not feasible, and to refer to the immunosuppressant product label for further administration if co-administered. However, given several post-authorization reports of hospitalizations for adverse reactions

(including acute kidney injury) associated with elevated tacrolimus levels in patients who were co-administered tacrolimus and PAXLOVID without close monitoring of immunosuppressant serum concentrations, these revisions are being added for further clarity.

- The systemic corticosteroids drug class listing and clinical comment is being revised as some of the listed drugs are not available for systemic administration and to note that the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. In addition, prednisone is being removed from the listed corticosteroids with an established and other potentially significant drug interaction and instead being named as an alternative corticosteroid that can be considered for use with PAXLOVID for consistency with labels for other products that only contain 100 mg of ritonavir per dose.

Similar revisions are being made to the PAXLOVID Fact Sheet for Patients, Parents, and Caregivers and the Patient Eligibility Screening Checklist Tool for Prescribers for consistency with the Fact Sheet for Healthcare Providers.

3. To Update the Fact Sheet for Healthcare Providers with Information on Viral RNA Rebound in the Clinical Trial EPIC-HR

A "Viral RNA Rebound" subsection is being added to Section 12.4 of the PAXLOVID Fact Sheet for Healthcare Providers to communicate the results of analyses conducted both by the Sponsor and independently by FDA on rebounds in SARS-CoV-2 RNA levels in NP/nasal swab samples after treatment cessation in both PAXLOVID and placebo recipients in the pivotal clinical trial EPIC-HR. Anecdotal reports of viral RNA rebound with PAXLOVID use in the EUA setting have garnered attention in the media and in public forums; therefore, a summary of available data from the double-blinded, randomized, placebo-controlled trial EPIC-HR is provided to better inform healthcare providers about this issue. Please see the full separate clinical virology review by Patrick Harrington, Ph.D. for more details.

4. To Revise the Patient Fact Sheet to Minimize Patient Medication Errors

The Fact Sheet for Patients, Parents, and Caregivers is being revised due to post-authorization reports of two types of medication errors. First, there have been a number of reports of PAXLOVID being prescribed to patients who are on concomitant medications that are contraindicated or not recommended for use with PAXLOVID. Consequently, the language in the "What should I tell my healthcare provider before I take PAXLOVID" section has been reorganized to emphasize the risk of serious side effects due to drug interactions with PAXLOVID. Second, there have been over 140 reports of a suspected wrong dose error. Of an analyzed subset, most occurred during patient administration

and often involved patients taking the wrong tablets, and several patients said the patient fact sheet and instructions on the packaging were confusing. Consequently, the “How do I take PAXLOVID” section is being revised to include that there are 2 different dose packs (based on renal function), to emphasize that the tablets are taken together 2 times each day for 5 days, and to show a picture of the dose packs with instructions on where to find the morning and evening doses.

Summary of Fact Sheet Revisions:

- Section 1 of the Fact Sheet for Healthcare Providers (EMERGENCY USE AUTHORIZATION) was updated to reference the new CDC website for [Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals](#), rather than the prior link which was intended for the general public ([People with Certain Medical Conditions](#)).
- Section 2.4 of the Fact Sheet for Healthcare Providers (Important Drug Interactions with PAXLOVID) was reordered and revised to include the following statement: “Interacting drugs listed in the Fact Sheet are a guide and not considered a comprehensive list of all possible drugs that may interact 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 such as ritonavir.”
- Section 4 of the Fact Sheet for Healthcare Providers (CONTRAINDICATIONS) was modified as follows:
 - The following statement was added: “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 such as ritonavir.”
 - The following drugs were added to the list of drugs that are contraindicated due to being highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions: silodosin, eplerenone, ivabradine, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, voclosporin, flibanserin, and tolvaptan
 - The following drugs were added to the list of drugs that are contraindicated due to being potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance: primidone and lumacaftor/ivacaftor

- Section 5.1 of the Fact Sheet for Healthcare Providers (Risk of Serious Adverse Reactions Due to Drug Interactions) was modified to add the following sentence: “Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.”
- Section 6.2 of the Fact Sheet for Healthcare Providers (Post-Authorization Experience) was modified to add the following adverse reactions identified during post-authorization use of PAXLOVID: abdominal pain, nausea, and malaise
- Section 7.1 of the Fact Sheet for Healthcare Providers (Potential for PAXLOVID to Affect Other Drugs) was minorly edited to emphasize that ritonavir is a strong CYP3A inhibitor.
- Section 7.3 of the Fact Sheet for Healthcare Providers (Established and Other Potentially Significant Drug Interactions) was modified as follows:
 - The text above the table was revised to provide a suggestion for other resources that can be used to find comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor.
 - Table 1 was revised to:
 - Add the following drugs: silodosin, eplerenone, ivabradine, voclosporin, lomitapide, elvitegravir, ubrogepant, finerenone, naloxegol, flibanserin, tolvaptan, primidone, lumacaftor/ivacaftor, tamsulosin, rifapentine, aliskiren, ticagrelor, vorapaxar, clopidogrel, ivacaftor, elvitegravir/tenofovir/efavirenz, elvitegravir/tenofovir/emtricitabine, everolimus, rimegepant, hydrocodone, oxycodone, suvorexant, tadalafil, avanafil, vardenafil, and sildenafil when used for erectile dysfunction (already included when used for pulmonary arterial hypertension).
 - Remove the following drugs: propoxyphene, bepridil, amprenavir, fosamprenavir, indinavir, nelfinavir, saquinavir, didanosine, delavirdine, raltegravir, and prednisone
 - Revise the clinical comments related to immunosuppressants and corticosteroids and make additional small edits.
- Section 12.4 of the Fact Sheet for Healthcare Providers (Microbiology) was revised to add a section on Viral RNA Rebound. This section reads as follows:

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients,

irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

- The Fact Sheet for Patients, Parents, and Caregivers was revised as follows:
 - The language in the “What should I tell my healthcare provider before I take PAXLOVID” section has been reorganized to emphasize the risk of serious side effects due to drug interactions with PAXLOVID.
 - The language in the “How do I take PAXLOVID” section was revised to include that there are 2 different dose packs (based on renal function), to emphasize that the tablets are taken together 2 times each day for 5 days and to show a picture of the dose packs with instructions on where to find the morning and evening doses.
 - The listing of medications under Do not take PAXLOVID if...you are taking any of the following medicines” was expanded to include the drugs being added to the list of contraindicated drugs and to reformat the list into several columns.
 - Abdominal pain, nausea, and feeling generally unwell were added to the possible side effects of PAXLOVID section.

A Dear Healthcare Provider Letter was also created to communicate the additions to the list of contraindicated drugs in the Fact Sheet for Healthcare Providers and to emphasize the need to assess for drug interactions.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 105 as outlined above in order to best protect public health and to provide health care providers and patients with the most current information about PAXLOVID. The analysis of benefits and risks that underlies the authorization of EUA 105 remains unchanged.

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/

STEPHANIE B TROY
06/28/2022 10:38:55 AM

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DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW

EUA# 000105 SDNs: 118,130,131,136, 147, 154, 158, 159 DATE REVIEWED: 6/24/2022

Reviewer: Patrick Harrington, PhD.

Assigned/Reviewed SDNs:

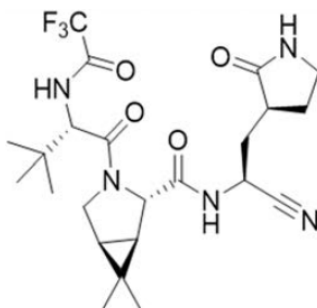
SDN	eCTD#	Rec'd Date	Assigned Date	Content
118	0115	4/26/2022	4/27/2022	Response to 4/22/22 request related to post-tx viral RNA rebound
130	0126	5/10/2022	5/10/2022	Response to 5/6/22 request for sponsor feedback on preliminary FDA analyses of viral RNA rebound
131	0127	5/11/2022	5/11/2022	Analysis of rebound in viral test results in "real world" database
136	0132	5/19/2022	5/20/2022	Response to 5/18/22 request regarding NP vs. nasal swab sampling
147	0143	6/6/2022	6/7/2022	Proposed revisions to HCP Fact Sheet
154	0149	6/16/2022	6/17/2022	Proposed revisions to HCP Fact Sheet
158	0153	6/23/2022	6/23/2022	Proposed revisions to HCP Fact Sheet
159	0154	6/24/2022	6/27/2022	Proposed revisions to HCP Fact Sheet

Sponsor: Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755
Karen Baker, Director, Pfizer Global Regulatory Affairs

Product Names: nirmatrelvir (PF-07321332, PAXLOVID™; coadministered with ritonavir)

Chemical Name: 1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

Structure:



NIRMATRELVIR (PF-07321332)

Molecular Formula: C₂₃H₃₂F₃N₅O₄

Molecular Weight: 499.54 daltons

Drug Category: Antiviral

Indication: Treatment of mild-to-moderate COVID-19

Dosage Form/Route of administration: nirmatrelvir 150 mg tablet, co-administered with ritonavir (PK enhancer) 100 mg tablet / oral

Supporting documents: IND 153517

Abbreviations: 3CLpro, 3C-like protease; CoV, coronavirus; Mpro, main protease; NIR/r, nirmatrelvir/ritonavir; nsp, nonstructural protein; NP, nasopharyngeal; SARS, severe acute respiratory syndrome; VL(R), viral load (rebound)

1. BACKGROUND

Nirmatrelvir/ritonavir (NIR/r, PAXLOVID™, PF-07321332/r; EUA 000105 and IND 153517) received FDA Emergency Use Authorization on 12/22/2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing 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.

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NIR is a reversible competitive inhibitor of the SARS-CoV-2 main protease (Mpro), also known as 3C-like protease (3CLpro) or nsp5 protease.

This set of submissions includes the sponsor's analyses and responses to DAV requests related to recent public reports of virologic and/or symptomatic "rebounds" following PAXLOVID treatment. In late April 2022, the Division became aware of case reports and stories in the press and social media related to patients who experienced symptomatic recovery during PAXLOVID treatment, but after stopping the 5-day course of treatment experienced "relapses" in COVID-19 symptoms which were coincident with rebounds in qualitative or quantitative viral RNA, antigen or virus detection in upper respiratory tract samples (e.g., see [Gupta et al., 2022](#); [Charness et al., 2022](#); [Carlin et al., 2022](#); [Washington Post 4/27/2022 article](#)). These cases have occurred in immunocompetent, vaccinated individuals, indicating that the phenomenon is not attributed to immune deficiency. Furthermore, there has been no reported evidence that these cases are related to emergence of NIR-resistant virus. These reports have raised concerns and some speculation that PAXLOVID treatment may suppress virus replication in a manner that delays the development of a functional host immune response that is ultimately responsible for clearing the infection, and that a longer treatment duration or re-treatment of "relapse" cases may be needed for optimal efficacy and to minimize the risk of SARS-CoV-2 transmission from treated individuals.

This review summarizes post-hoc analyses conducted by the sponsor, and additional analyses independently conducted by FDA, to investigate the frequency, role of PAXLOVID treatment, and the potential clinical relevance of post-treatment SARS-CoV-2 RNA rebound using available virology, genotypic resistance and clinical data from the Phase 2/3 C4671005 (EPIC-HR) trial. The sponsor also investigated this topic using electronic health record data from PAXLOVID-prescribed patients. As described below, post-treatment viral RNA rebound could be observed in both treated and untreated infected populations and thus was not specifically linked to drug treatment.

Clinical trial C4671005 evaluated PAXLOVID safety and efficacy in non-hospitalized, unvaccinated, high-risk adult participants with mild-to-moderate COVID-19 and demonstrated a 5-day course of PAXLOVID treatment was associated with an ~88% reduction in the risk of COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo.

Nasopharyngeal (NP) swab samples, and in some cases nasal mid-turbinate swab samples (discussed below) 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. Viral RNA levels were measured at a central laboratory ((b) (4)) 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 (nsp12) and nucleocapsid (N) genes. The assay has a lower limit of quantification (LLOQ) of 100 (2 log₁₀) copies/mL. Note that based on previously reported data, ~99% of subjects enrolled in the trial with available viral sequencing data were infected with a SARS-CoV-2 Delta variant.

See the [12/22/2021 multidisciplinary review of EUA 000105](#), additional Clinical Virology analyses from the Original EUA 000105 submission package ([EUA000105.000](#)), and the subsequent Clinical Virology review of [EUA 000105 SDNs 46-92](#) for detailed analyses of efficacy and resistance from this clinical trial C4671005.

2. SPONSOR'S ANALYSES OF VIRAL RNA REBOUND IN STUDY C4671005

Identification of Subjects with Post-treatment SARS-CoV-2 RNA Rebound

The sponsor's analyses of viral RNA rebound in clinical trial C4671005 (EPIC-HR) were summarized primarily in a slide deck submitted in [SDN 118](#). Note that the terms "viral load (VL)" and "viral load rebound (VLR)" are included in some places below as this is the terminology used by the sponsor. However, we generally do not view viral RNA levels in NP or nasal swab samples as measures of "viral load." Viral RNA levels in these

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samples could be considered a measure of viral shedding in the upper respiratory tract, but they do not necessarily reflect virus or viral RNA levels in other anatomical compartments such as the lungs, nor should they be considered a measure of the overall body burden of virus or viral nucleic acid in a manner like blood plasma viral load in chronic infections like HIV or HCV.

Note that 95.3% of all viral RNA results reported in the full dataset from study C4671005 were derived from NP swab samples, while 4.5% were reported from “NOSTRIL” swab samples (remaining ~0.2% of results with unspecified sampling location). For analysis purposes all of these results were combined. The sponsor clarified in [SDN 136](#) that Day 1 and Day 5 study visits were to occur in person and include NP swab sample collections, while some flexibility was allowed for Day 3, Day 10 and Day 14 visits. During an in-person visit, whether conducted in-clinic or by home health, an NP swab was to be collected by the healthcare provider. When visits were conducted by telemedicine, participants self-collected a nasal swab (i.e., “NOSTRIL” sampling site), which involved sampling both nostrils with the same swab up to ~2 cm into the nostrils until slight resistance is felt, consistent with a mid-turbinate swab ([CDC 2022](#)). Self-collected swabs were to be refrigerated until pickup by courier on the same day of collection, after which they were shipped to the central laboratory on dry ice. In many cases, sites chose to conduct an in-person visit even when telemedicine was an option, and as a result, NP collections also predominantly occurred at Day 3, Day 10 and Day 14. For Day 10 and Day 14 analysis visits, 90.3% and 92.1% of reported viral RNA results, respectively, were from NP swab samples. Note that viral RNA levels tend to be higher in NP samples compared to nasal mid-turbinate or other upper respiratory tract samples, and this was the case in the sponsor’s dataset (analysis not shown), so inclusion of the Day 10 and Day 14 non-NP data in these analyses would not inflate the calculated rate of post-treatment viral RNA rebound.

The sponsor defined post-treatment “viral load rebound (VLR)” as follows:

- If Day 14 viral RNA result is available:
 - Day 14 viral RNA change from Day 5 ≥ 0.5 Log₁₀ copies/mL
 - Day 14 viral RNA ≥ 2.7 Log₁₀ copies/mL
- If Day 14 viral RNA result is not available:
 - Day 10 viral RNA change from Day 5 ≥ 0.5 Log₁₀ copies/mL
 - Day 10 viral RNA ≥ 2.7 Log₁₀ copies/mL

Based on these criteria, the sponsor reported a viral RNA rebound rate of 2.1% (23/1106) for subjects who received PAXLOVID, and 1.5% (17/1110) for subjects who received placebo. Viral RNA kinetics for these individual subjects are shown in Figure 1 (Sponsor’s [4/26/22 response document](#), pg. 18).

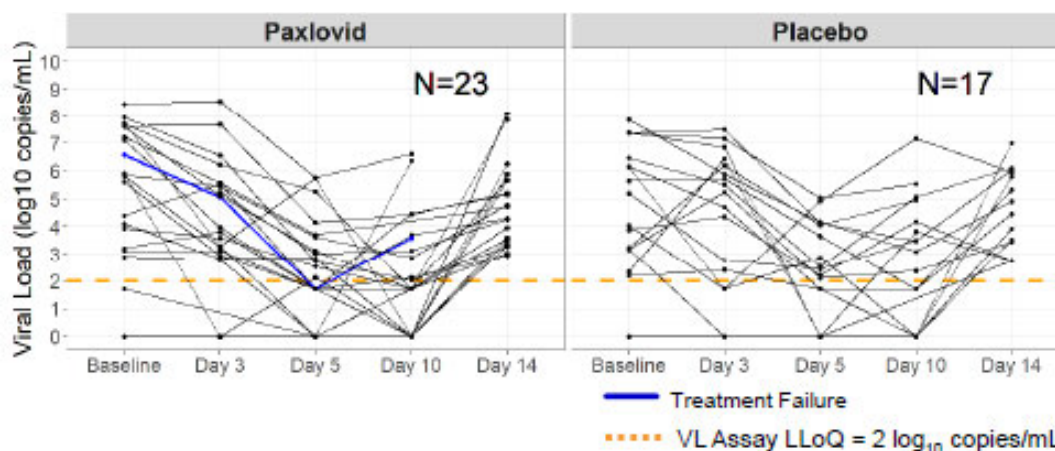


Figure 1. Viral RNA levels in NP/nasal swab samples for individual subjects identified by sponsor as having post-treatment viral RNA rebound in study C4671005 (EPIC-HR).

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Note that this Day 14-focused criteria for viral RNA rebound would not capture earlier, transient rebounds in viral RNA levels that were observed on Day 10 but not on Day 14. Also, the definition would not capture rebounds in viral RNA levels from Day 5 <LLOQ (<2 log₁₀ copies/mL) if the RNA level at the assessed post-treatment timepoint was >LLOQ but <2.7 log₁₀ copies/mL. Also note that the sponsor calculated the “rates” of viral RNA rebound using all enrolled and treated subjects as denominators, not just those with viral RNA results available on Day 5 and Day 10 or Day 14.

The sponsor commented further in [SDN 130](#) that the RT-PCR assay is likely too sensitive to detect clinically relevant “viral load rebound” as it is highly likely that it is detecting residual viral RNA fragments from the infection itself, which the sponsor will investigate further in cell culture infectivity analyses. As further justification for the sponsor’s analysis parameters, the sponsor’s analyses were aligned with the lower limit of viral RNA for sequencing analyses and were focused on investigating the relationship between viral RNA rebound and NIR resistance. The sponsor also commented that infections that had resolved by Day 14 (i.e., those with earlier transient rebounds no longer detected at Day 14) were not considered as clinically meaningful or biologically critical for investigating the role of NIR resistance.

Additional analysis parameters for identification of post-treatment viral RNA rebound were investigated in independent FDA analyses, which are described later in this review. While most of the independent FDA analyses focused on a more sensitive definition of post-treatment viral RNA rebound, in this reviewer’s opinion the clinical relevance of viral RNA rebound identified by any criteria is unclear, and thus there is no single established “ideal” set of criteria for identifying patients with post-treatment viral RNA rebound.

Investigations into Relationship between Viral RNA Rebound, Drug Exposures, Clinical Outcomes, and Nirmatrelvir Resistance

The sponsor conducted an exploratory analysis to determine if viral RNA rebound was associated with reduced NIR exposure. In subjects with viral RNA rebound (sponsor-defined), NIR exposures generally did not differ from the overall PAXLOVID treatment population (Figure 2; Sponsor’s [4/26/22 response document](#), pg. 19).

*QC/stats pending
All Participants in Safety Analysis:

DAY	TIME	N	Mean(STD) ng/mL
1	1H	240	2186 (2107)
5	0MIN	444	2964 (2851)

VLR Participants:

DAY	TIME	N	Mean(STD) ng/mL
1	1H	22	1875 (2007)
5	0MIN	22	2864 (3885)

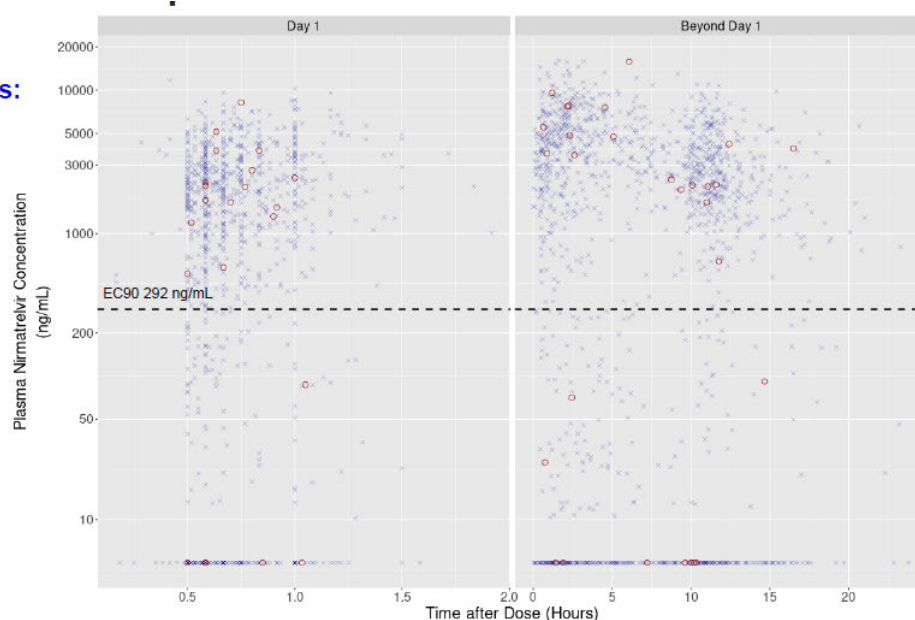


Figure 2. Nirmatrelvir plasma exposures in PAXLOVID-treated subjects with and without post-treatment viral RNA rebound (sponsor-defined) in study C4671005. In the charts presumably the red circles indicate subjects with viral RNA rebound. The noted nirmatrelvir EC₉₀ value (292 ng/mL, 585 nM) refers to the unbound EC₉₀ value against SARS-CoV-2 in differentiated normal human bronchial epithelial (dNHBE) cells.

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Post-treatment viral RNA rebound was not associated with recurrence of moderate-severe symptoms (Figure 3; Sponsor's [4/26/22 response document](#), pg. 21). Only one PAXLOVID treated subject (b) (6) had moderate-severe symptoms temporally associated with viral RNA rebound, while 17 other PAXLOVID treated subjects (including hospitalized subject (b) (6)) had moderate-severe symptoms that were not temporally associated but rather preceded and in most cases had resolved by the time of viral RNA rebound. Note that these analyses did not consider mild symptoms.

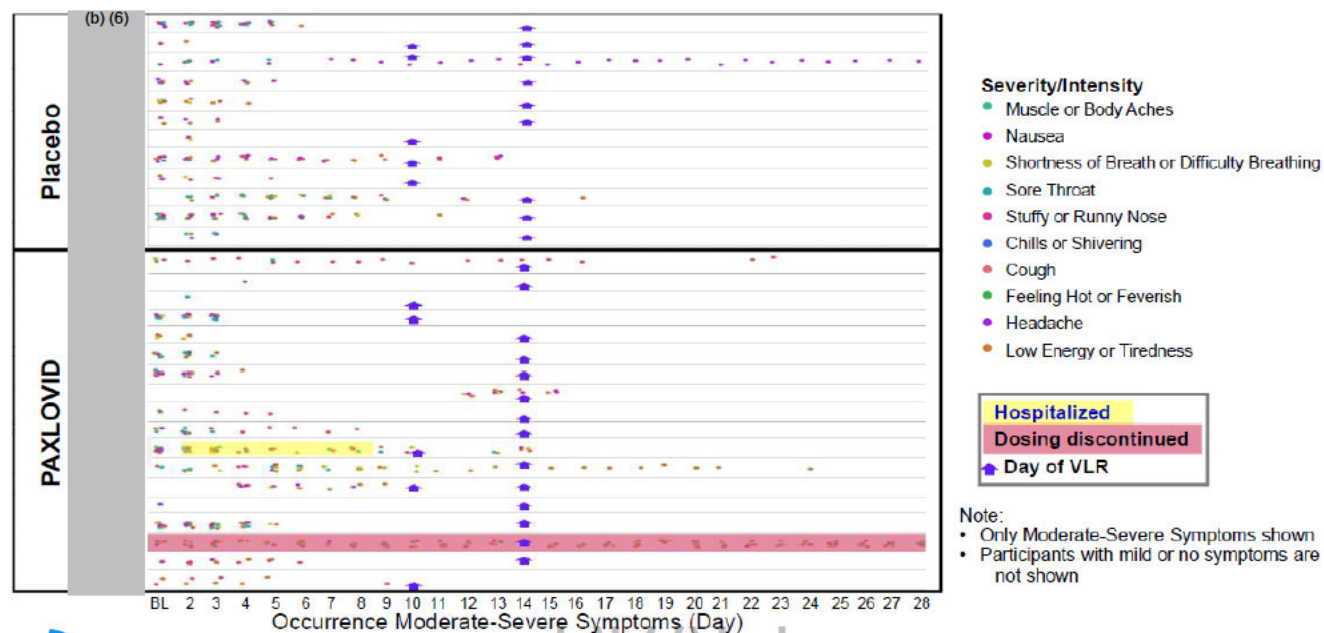


Figure 3. Timing of moderate-severe symptoms and post-treatment viral load rebound (VLR, sponsor-defined) in study C4671005 (EPIC-HR).

The primary clinical endpoint of hospitalization/death was not associated with post-treatment viral RNA rebound (Figure 4; Sponsor's [4/26/22 response document](#), pg. 22). Only 1 PAXLOVID treated subject (b) (6) who was hospitalized met the sponsor's definition of post-treatment viral RNA rebound, and hospitalization first occurred on Day ~2, preceding the timing of viral RNA rebound. Subject (b) (6) did not meet the sponsor's definition of viral RNA rebound but did show an increase in viral RNA level from Day 10 to Day 14; the subject was hospitalized on Day ~8, again preceding the timing of viral RNA rebound.

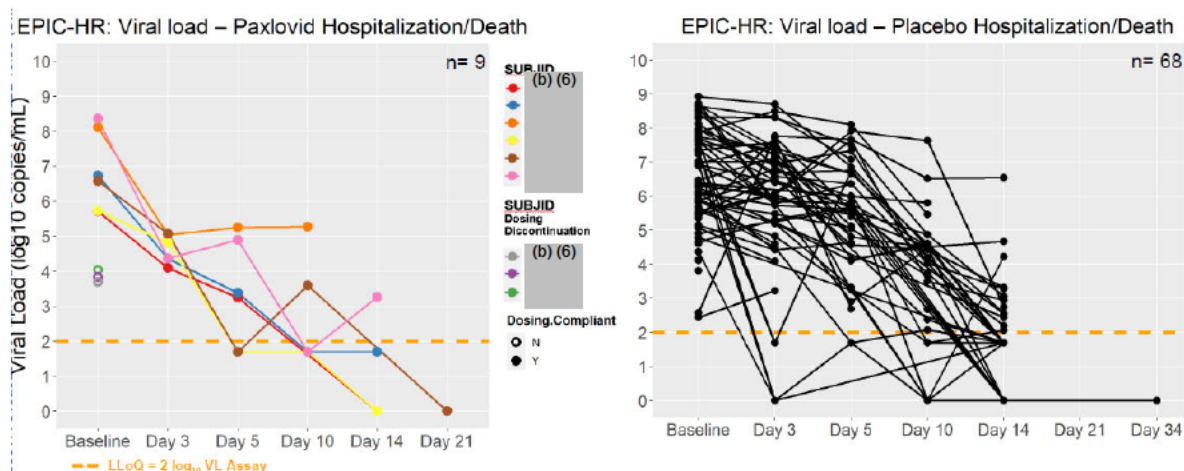


Figure 4. Viral RNA levels in NP/nasal swab samples in subjects who experienced hospitalization or death in study C4671005 (EPIC-HR).

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The sponsor also reported that viral RNA rebound was not associated with the emergence of amino acid substitutions in SARS-CoV-2 Mpro or Mpro cleavage sites (Figure 5; Sponsor's [4/26/22 response document](#), pg. 26). Among subjects with sponsor-defined post-treatment viral RNA rebound and with available viral sequence analysis data, any Mpro or Mpro cleavage site treatment-emergent amino acid substitution was detected in 33% (6/18) of PAXLOVID treated subjects and 31% (4/13) of placebo treated subjects. No treatment-emergent substitutions were detected at a NIR contact residue or other known or potentially important resistance-associated position in Mpro. The sponsor noted additional viral infectivity and phenotypic analyses are ongoing.

Viral Sequencing from participant swabs, virus isolation ongoing

	Paxovid VLR (N = 23)	Placebo VLR (N = 17)
Matched D1 & D10/D14	18	13
NO D10/D14 TEM	12	9
with D10/D14 TEM	6	4

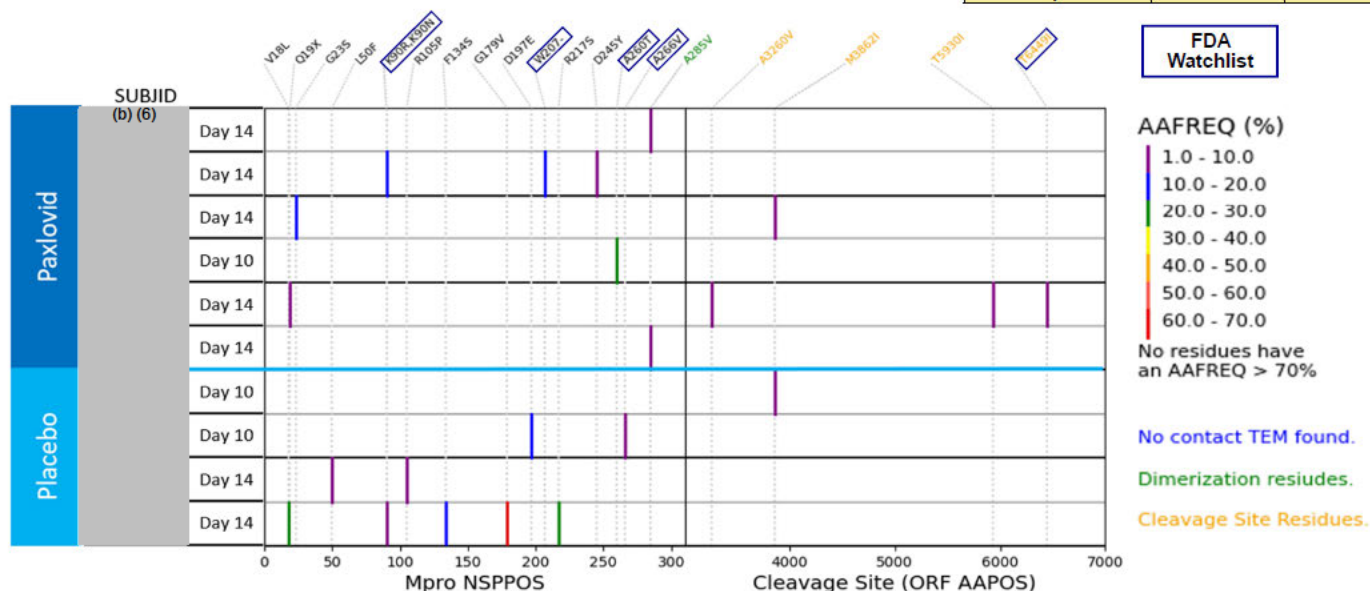


Figure 5. Treatment-emergent amino acid substitutions (5% frequency cutoff) detected in SARS-CoV-2 Mpro or Mpro cleavage sites in NP/nasal swab samples from subjects with sponsor-defined post-treatment viral RNA rebound in study C4671005 (EPIC-HR). “Treatment-emergent mutation (TEM)” refers to any treatment-emergent amino acid substitution in Mpro or an Mpro cleavage site.

The sponsor also reviewed concomitant medications and concluded that there were no particular patterns of concomitant medications that appear to have direct or indirect implications for post-treatment viral RNA rebound.

In summary, in the sponsor’s analyses of clinical trial C4671005, post-treatment viral RNA rebound was observed in a subset of PAXLOVID and placebo treated subjects, and the sponsor found no association between post-treatment viral RNA rebound and hospitalization or death, moderate symptoms, drug resistance, nirmatrelvir exposures, or concomitant medications.

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3. INDEPENDENT FDA ANALYSES OF VIRAL RNA REBOUND IN STUDY 4671005

Identification of Subjects with Post-treatment SARS-CoV-2 RNA Rebound

Viral RNA data reported from Study 4671005 were independently analyzed to characterize the frequency and potential clinical relevance of rebounds in viral RNA levels following treatment with PAXLOVID or placebo. These analyses used the [ADMC](#) dataset reported in SDN 65.

As previously documented ([EUA000105.000](#); [EUA 000105 SDNs 46-92](#)), treatment with PAXLOVID was, on average, associated with a consistent and more rapid decline in viral RNA levels compared to placebo, with a $\sim 0.8 \log_{10}$ copies/mL greater mean decline in viral RNA levels through Day 5/end-of-treatment (Figure 6-top, FDA analysis). However, it should be noted that there was substantial inter- and intra-subject variability in viral RNA levels over time, with evidence of fluctuations in viral RNA levels for individual subjects throughout the study period (Figure 6-bottom, FDA analysis).

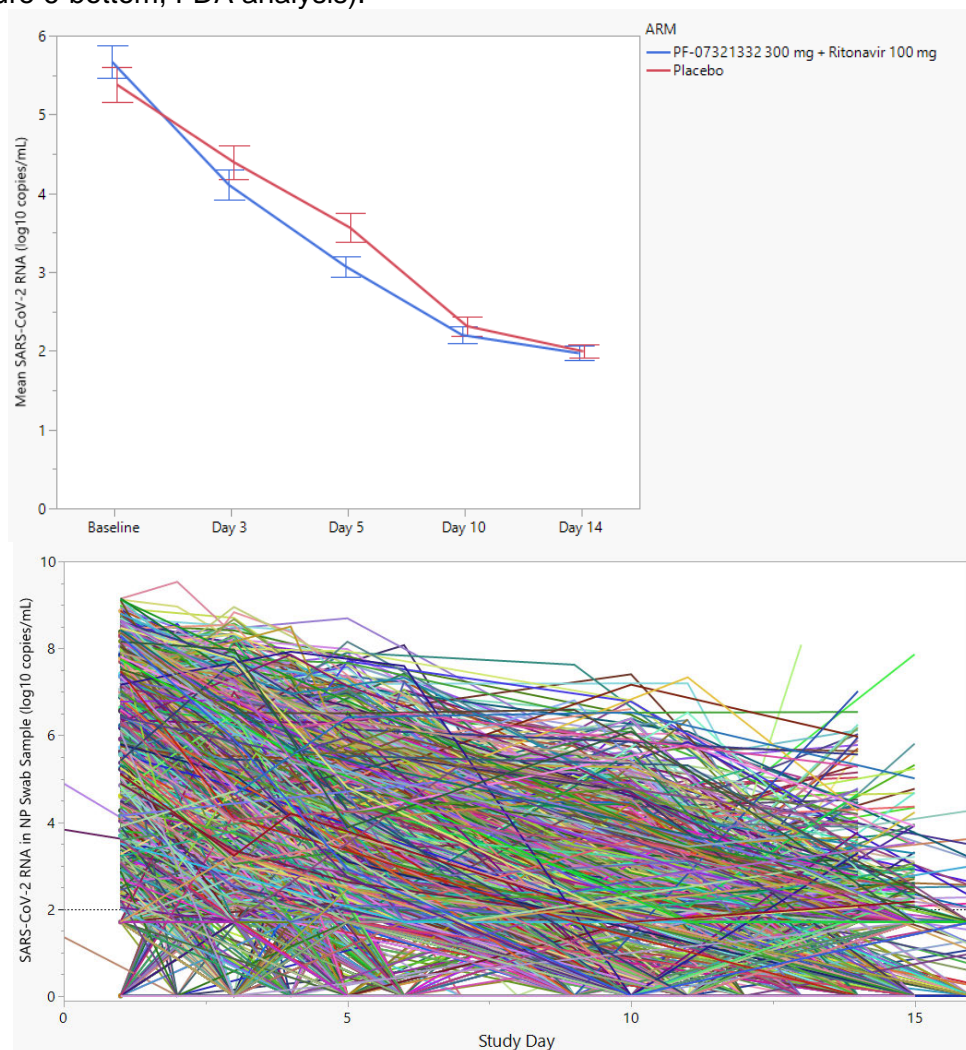


Figure 6. Mean SARS-Cov-2 RNA levels within each analysis visit window for PAXLOVID (i.e., PF—07321332 + ritonavir) and placebo treated subjects (top), and results by specific Study Day for individual subjects (bottom). Dashed horizontal line indicates assay LLOQ (2 log₁₀ copies/mL).

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The following definitions of viral RNA rebound were considered for identification of post-treatment rebound:

Day 10 (LLOQ): Day 5 <LLOQ, Day 10 ≥LLOQ

Day 10 (LLOQ-2.5): Day 5 <LLOQ, Day 10 ≥2.5 (LLOQ + 0.5 log₁₀)

Day 10 (0.5): Day 5 ≥LLOQ, Day 10 ≥0.5 log₁₀ copies/mL increase from Day 5

Day 10 (LLOQ/0.5 Combined): Day 10 (LLOQ) PLUS Day 10 (0.5)

Day 10 (LLOQ-2.5/0.5 Combined): Day 10 (LLOQ-2.5) PLUS Day 10 (0.5)

Day 14 (LLOQ): Day 5 <LLOQ, Day 14 ≥LLOQ

Day 14 (LLOQ-2.5): Day 5 <LLOQ, Day 14 ≥2.5 (LLOQ + 0.5 log₁₀)

Day 14 (0.5): Day 5 ≥LLOQ, Day 14 ≥0.5 log₁₀ copies/mL increase from Day 5

Day 14 (LLOQ/0.5 Combined): Day 14 (LLOQ) PLUS Day 14 (0.5)

Day 14 (LLOQ-2.5/0.5 Combined): Day 14 (LLOQ-2.5) PLUS Day 14 (0.5)

Day 10/14 (LLOQ): Day 5 <LLOQ, Day 10 OR Day 14 ≥LLOQ

Day 10/14 (LLOQ-2.5): Day 5 <LLOQ, Day 10 OR Day 14 ≥2.5 (LLOQ + 0.5 log₁₀)

Day 10/14 (0.5): Day 5 ≥LLOQ, Day 10 OR Day 14 ≥0.5 log₁₀ copies/mL increase from Day 5

Day 10/14 (LLOQ/0.5 Combined)*: Day 10/14 (LLOQ) PLUS Day 10/14 (0.5)

Day 10/14 (LLOQ-2.5/0.5 Combined): Day 10/14 (LLOQ-2.5) PLUS Day 10/14 (0.5)

**Most sensitive analysis of post-treatment viral RNA rebound: Any evidence of viral RNA rebound from Day 5 to Day 10 or 14, based on <LLOQ to ≥LLOQ, or 0.5 log₁₀ copies/mL increase from Day 5.*

In these analyses all denominators were based on the numbers of subjects with data at the timepoint(s) under consideration. The purpose of the LLOQ-2.5 analyses (i.e., <LLOQ on Day 5, followed by increase to 0.5 log₁₀ above LLOQ on Day 10 or Day 14) was to account for possible assay variability around the assay LLOQ value (2.0 log₁₀ copies/mL). While the data were analyzed with all of these definitions to assess the impact of different definitions on the estimated rate of viral RNA rebound, most subsequent analyses used the “Day 10/14 (LLOQ/0.5 Combined)” definition, which identified subjects with any evidence of viral RNA rebound from Day 5 (End-of-Treatment) to Day 10 or 14, based on RNA levels <LLOQ at Day 5 to ≥LLOQ on either Day 10 or Day 14, or, a 0.5 log₁₀ copies/mL increase from Day 5 level on either Day 10 or Day 14.

The calculated rates of post-treatment viral RNA rebound are summarized in Table 1 and Figure 7 (FDA analyses). Based on the most sensitive Day 10/14 (LLOQ/0.5 Combined) definition, post-treatment viral RNA rebound could be observed in 8.1% (80/1106) of PAXLOVID recipients and 5.4% (53/1110) of placebo recipients.

We also analyzed the same viral RNA dataset using the sponsor’s definition of “viral load rebound” and confirmed the sponsor’s reported rate of rebound: 2.1% (23/1106) for PAXLOVID recipients and 1.5% (17/1110) for placebo recipients (2.3% and 1.7%, respectively, with denominators based on subjects with available viral RNA data at Day 5 and Day 10 or 14). Thus, the FDA Day 10/14 (LLOQ/0.5 Combined) definition identified approximately 3- to 4-fold more cases of post-treatment viral RNA rebound compared to the sponsor’s definition.

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Table 1. Proportions of subjects with post-treatment viral RNA rebound according to analysis definition.

	PAXLOVID (N=1106)	Placebo (N=1110)
Day 10		
N	929	914
Day 10 (LLOQ)	26 (2.8%)	13 (1.4%)
Day 10 (LLOQ-2.5)	20 (2.2%)	7 (0.8%)
Day 10 (0.5)	32 (3.4%)	27 (3.0%)
Day 10 (LLOQ/0.5 Combined)	58 (6.2%)	40 (4.4%)
Day 10 (LLOQ-2.5/0.5 Combined)	52 (5.6%)	34 (3.7%)
Day 14		
N	948	950
Day 14 (LLOQ)	14 (1.5%)	9 (0.9%)
Day 14 (LLOQ-2.5)	10 (1.1%)	6 (0.6%)
Day 14 (0.5)	11 (1.2%)	8 (0.8%)
Day 14 (LLOQ/0.5 Combined)	25 (2.6%)	17 (1.8%)
Day 14 (LLOQ-2.5/0.5 Combined)	21 (2.2%)	14 (1.5%)
Day 10 OR Day 14		
N	990	980
Day 10/14 (LLOQ)	37 (3.7%)	21 (2.1%)
Day 10/14 (LLOQ-2.5)	28 (2.8%)	12 (1.2%)
Day 10/14 (0.5)	43 (4.3%)	32 (3.3%)
Day 10/14 (LLOQ/0.5 Combined)	80 (8.1%)*	53 (5.4%)*
Day 10/14 (LLOQ-2.5/0.5 Combined)	71 (7.2%)*	44 (4.5%)*

*p<0.05 Fisher's Exact Test PAXLOVID vs. Placebo
(note: did not test other data)

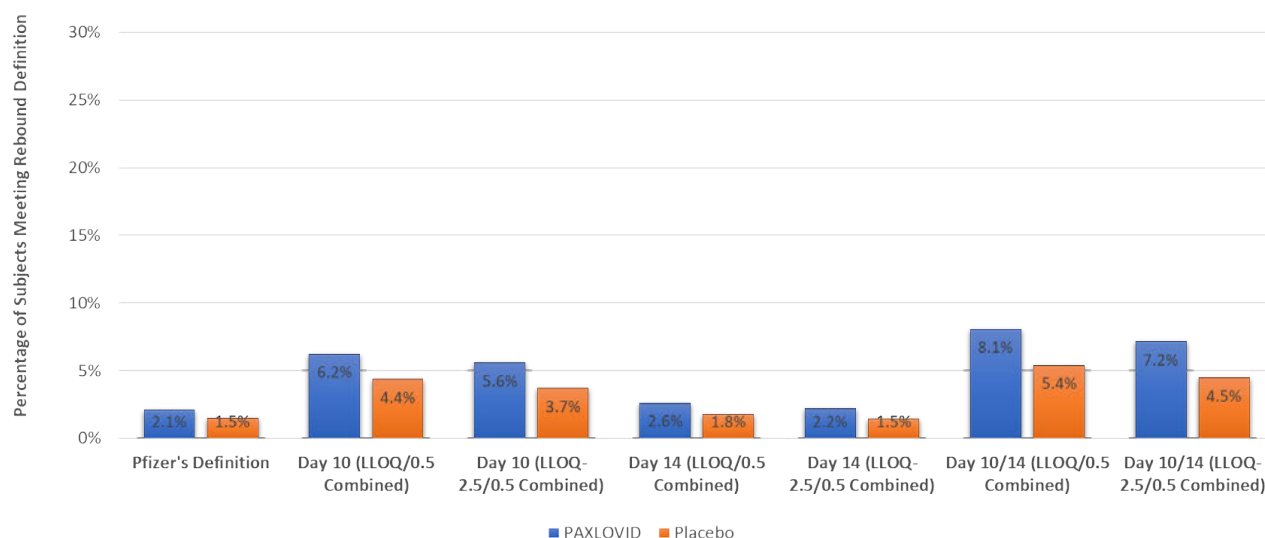


Figure 7. Proportions of subjects with post-treatment viral RNA rebound according to different analysis definitions.

Despite the overall similar rates of viral RNA rebound in the PAXLOVID and placebo groups across different definitions, the results based on the FDA Day 10/14 (LLOQ/0.5 Combined) analysis definition were significantly

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different between PAXLOVID and placebo recipients (8.1% versus 5.4%, respectively, $p=0.02$, Fisher's Exact test). Note that post-treatment viral RNA rebound definitions generally would not capture subjects with a slow or inapparent viral RNA decline through Day 5. Not surprisingly, nearly all subjects (94% across both arms [120/127, excl. 6 subjects w/o baseline result]) who met the FDA Day 10/14 (LLOQ/0.5 Combined) definition of post-treatment viral RNA rebound had a $\geq 1 \log_{10}$ copies/mL decline in viral RNA level from baseline to Day 5, or otherwise a Day 5 viral RNA level $< \text{LLOQ}$.

Table 2 (FDA analysis) summarizes the Day 5 virologic responses observed in the PAXLOVID and placebo groups. Consistent with previous analyses, subjects who received PAXLOVID were more likely to show a decline in viral RNA levels from baseline to Day 5. Therefore, it is possible that the higher proportion of PAXLOVID-treated subjects achieving a virologic response on Day 5 could contribute to a higher post-treatment (i.e., post-Day 5) viral RNA rebound rate. The sponsor also investigated and discussed this potential confounding factor in [SDN 130](#).

Table 2. Proportions of subjects with a viral RNA response from baseline to Day 5 (or Day 5 $< \text{LLOQ}$).

	PAXLOVID	Placebo
N	979	980
Day 5 RNA decline from baseline (median \log_{10} copies/mL)	2.19	1.34
Day 5 ≥ 1 log decline	644 (65.8%)	547 (55.8%)
Day 5 ≥ 1 log decline OR $< \text{LLOQ}$	896 (91.5%)	816 (83.3%)
Day 5 ≥ 2 log decline	519 (53.0%)	385 (39.3%)
Day 5 ≥ 2 log decline or $< \text{LLOQ}$	827 (84.5%)	698 (71.2%)

Note: Considering subjects who had paired Baseline/Day 5 data.

To address the confounding factor of different on-treatment virologic response rates, an additional analysis of post-treatment viral RNA rebound was conducted focusing on the subgroup of subjects who could be classified as virologic responders on Day 5. As shown in Table 3 (FDA analysis), when the analysis was restricted to Day 5 virologic responders, the post-treatment viral RNA rebound rates among PAXLOVID and placebo recipients narrowed and were no longer significantly different. In other words, among those who had a decline in viral RNA level from baseline to Day 5, or a Day 5 viral RNA $< \text{LLOQ}$, there was not a clear difference in the likelihood of viral RNA rebound after Day 5 between those who had received PAXLOVID versus those who received placebo. These results indicate that the greater Day 5 response rate in PAXLOVID recipients likely contributed to some of the difference in the calculated rebound rates between the overall PAXLOVID and placebo groups.

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Table 3. Post-treatment viral RNA rebound rates (LLOQ/0.5 Combined definition) according to Day 5 virologic responses.

	PAXLOVID	Placebo	P Value ²
All subjects (with Day 5 and Day 10/14 viral RNA data)	8.1% (80/990)	5.4% (53/980)	0.020
All subjects in Day 5 virologic response analysis ¹	7.7% (74/967)	5.5% (53/959)	0.066
Day 5 $\geq 1 \log_{10}$ copies/mL decline from baseline, OR $< \text{LLOQ}$ ¹	7.9% (70/884)	6.3% (50/798)	0.218
Day 5 $\geq 2 \log_{10}$ copies/mL decline from baseline, OR $< \text{LLOQ}$ ¹	7.5% (61/815)	6.1% (42/685)	0.308

¹Considering subjects who had paired Baseline/Day 5 data., plus either Day 10 or Day 14 data to assess post-treatment rebound

²Fisher's Exact Test

As further evidence that PAXLOVID treatment, regardless of any post-treatment viral RNA rebound, did not ultimately result in delayed clearance in viral RNA shedding, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA $< \text{LLOQ}$ at all analysis visits (Table 4, FDA analysis). Based on these results, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely detected from 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 4. Proportions of subjects with viral RNA $< \text{LLOQ}$ at each analysis visit.

	PAXLOVID	Placebo
Day 3	35.5% (369/1038)	34.1% (355/1040)
Day 5	47.4% (475/1002)	43.9% (439/1001)
Day 10	77.4% (765/989)	70.3% (676/962)
Day 14	89.1% (899/1009)	86.4% (869/1006)

Viral RNA levels for individual subjects identified as having post-treatment viral RNA rebound according to the sponsor's or FDA Day 10/14 (LLOQ/0.5 Combined) definitions are illustrated in Figure 8 (FDA analysis). Most of the differences in the calculated rates of viral RNA rebound between the sponsor's and FDA Day 10/14 (LLOQ/0.5 Combined) definitions are explained by subjects with transient viral RNA rebounds on Day 10 that were not observed on Day 14, which would not have been captured in the sponsor's definition. Of note, viral RNA rebound was detected more frequently on Day 10 relative to Day 14 in both the PAXLOVID and placebo groups.

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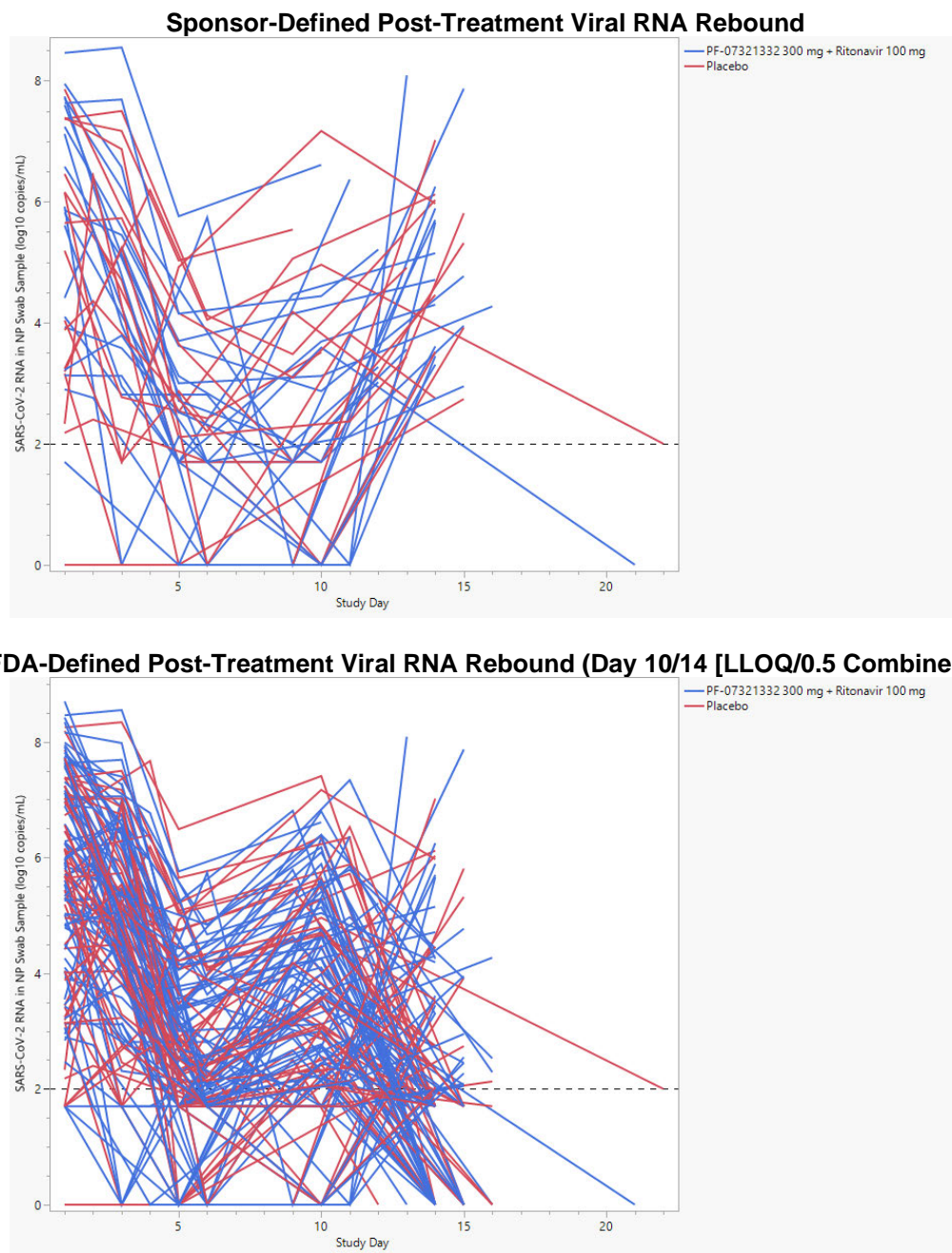


Figure 8. Viral RNA levels for individual subjects with post-treatment viral RNA rebound. Dashed horizontal line indicates assay LLOQ (2 log₁₀ copies/mL).

Investigations into Relationship between Viral RNA Rebound, Clinical Outcomes, and Nirmatrelvir Resistance

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28. Among the 133 subjects in the PAXLOVID and placebo arms who experienced post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition), 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 9 (FDA analysis) 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

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(Subject (b) (6)) 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, and the subject was not re-admitted to the hospital. One placebo treated subject (Subject (b) (6)) 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 reflects some of the natural variability in COVID-19 disease progression.

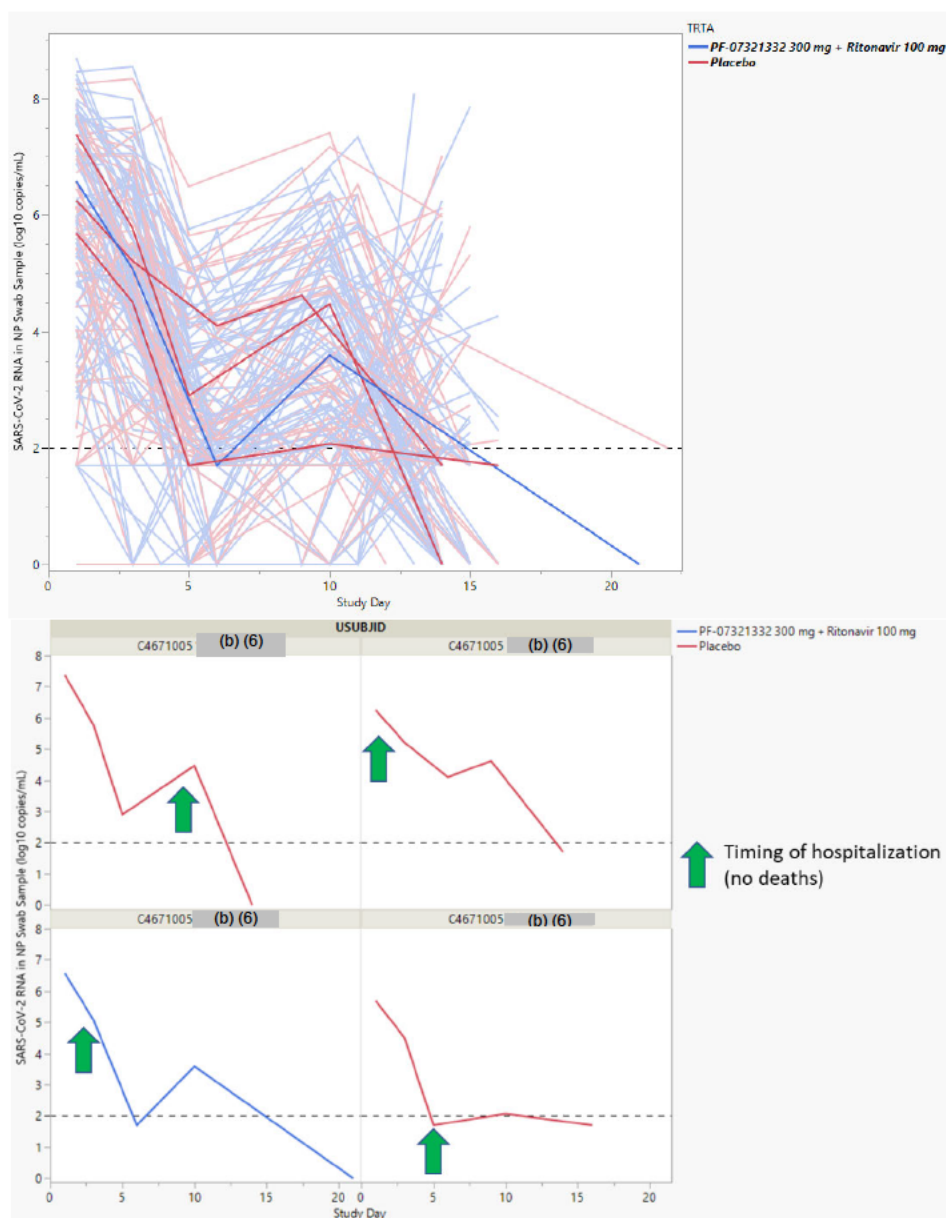


Figure 9. Viral RNA levels in subjects who experienced post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition) and reached the primary clinical endpoint of COVID-19-related hospitalization or death from any cause through Day 28. The top panel shows the 4 subjects with viral RNA rebound and COVID-19-related hospitalization (no deaths) in the foreground, with all other subjects with viral RNA rebound in the background. The bottom panels show the results for each of the 4 subjects relative to the timing of hospitalization. Dashed horizontal line indicates assay LLOQ (2 log₁₀ copies/mL).

Post-treatment viral RNA rebound was not associated with baseline immunosuppression or HIV-1 infection, although this was a small subgroup of subjects in the trial (n=6 PAXLOVID, n=8 placebo). Viral RNA results for

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the 14 subjects with baseline immunosuppression or HIV-1 infection are shown in Figure 10 (FDA analysis). 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.

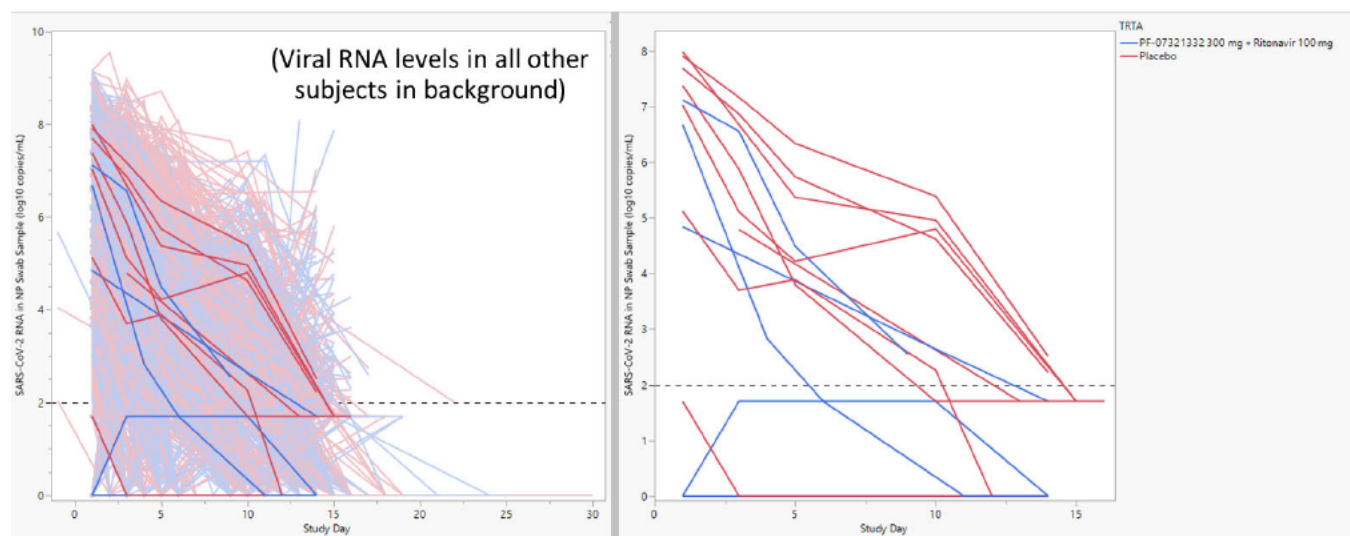


Figure 10. Viral RNA levels in subjects with baseline immunosuppression or HIV-1 infection. Dashed horizontal line indicates assay LLOQ (2 log₁₀ copies/mL).

Consistent with the sponsor's analyses, we did not find an association between post-treatment viral RNA rebound and evidence of NIR resistance based on viral sequencing data. As shown in Table 5 (FDA analysis), among subjects who experienced post-treatment viral RNA rebound, the detection of treatment-emergent, potential NIR resistance-associated substitutions was no more common among PAXLOVID recipients relative to placebo recipients. For these analyses, a 5% sensitivity cutoff was used to detect amino acid substitutions, and we focused on identifying treatment-emergent substitutions at Mpro amino acid positions that could be involved in NIR susceptibility and resistance based on one or more of the following criteria: (1) position in or near the NIR binding site (within ~5 angstroms), (2) position where substitution(s) have been shown to confer reduced phenotypic susceptibility to NIR, or (3) position where amino acid substitutions emerged in mouse hepatitis virus (MHV, surrogate coronavirus) selected for resistance to NIR. Two of these amino acid positions (186 and 189) were suspected of having a high degree of sequencing artifacts in previous resistance analyses from C4671005; therefore, analyses were conducted both including and excluding these positions. Note that viral sequencing data from the trial were not fully complete at the time of these analyses, so additional analyses will be conducted as more data become available.

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Table 5. Proportions of subjects with post-treatment viral RNA rebound (FDA Day 10/14 [LLOQ/0.5 Combined] definition) who had treatment-emergent amino acid substitutions detected at a potential nirmatrelvir resistance-associated position in Mpro.

	PAXLOVID	Placebo
All Mpro Positions of Interest ¹	43% (18/42)	44% (12/27)
All Mpro Positions of Interest, excluding 186/189 ²	7% (3/42)	15% (4/27)
¹ Positions near NIR binding site, where AA substitutions confer reduced phenotypic susceptibility, or where AA substitutions emerged in drug-selected MHV (15, 41, 49, 50, 54, 55, 126, 129, 135, 140, 141, 142, 143, 144, 145, 163, 164, 165, 166, 167, 168, 172, 186, 187, 188, 189, 190, 191, 192, 248) ² Positions 186 and 189 have a high frequency of changes suspected due to sequencing artifacts		

Viral RNA levels for each of the 7 subjects with a treatment-emergent, potential NIR resistance-associated substitution (excluding positions 186/189) are shown in Figure 11 (FDA analysis). Given that a comparable number of PAXLOVID and placebo recipients had one of these emergent amino acid substitutions detected, their emergence cannot clearly be attributed to PAXLOVID drug pressure and drug resistance. Nevertheless, the one PAXLOVID treated subject with treatment-emergent Mpro E166V (detected at a ~8% frequency) is noted as this has been flagged previously as being a potentially important resistance-associated substitution. Overall in C4671005, treatment-emergent E166V was detected in 3 PAXLOVID treated subjects and 0 placebo treated subjects, and in a biochemical assay an E166A substitution conferred a 33-fold reduction in NIR susceptibility. More recently, a preprint publication by [Zhou et al., 2022](#) reported E166V engineered into SARS-CoV-2 conferred 25-fold and 267-fold increases in nirmatrelvir EC₅₀ values in two different cell lines. Therefore, it is possible that in this one subject, post-treatment viral RNA rebound was associated with the emergence of a NIR resistance-associated substitution, but it is challenging to draw a firm conclusion given the single subject observation with a low frequency of detection, as well as the emergence of other potential NIR resistance-associated substitutions among placebo recipients.

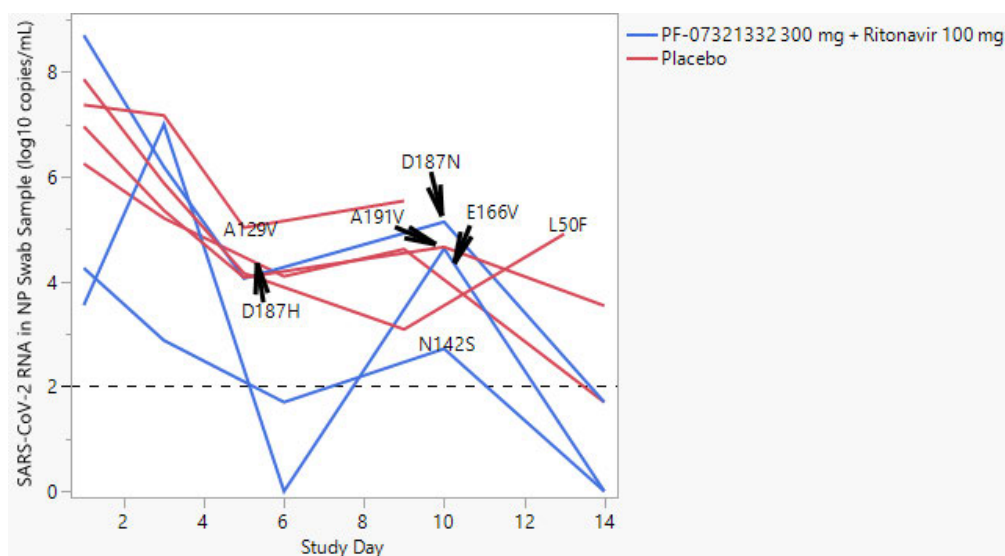


Figure 11. Viral RNA levels for individual subjects with treatment-emergent, potential nirmatrelvir resistance-associated amino acid substitutions detected in Mpro (excluding changes at positions 186/189). Dashed horizontal line indicates assay LLOQ (2 log₁₀ copies/mL).

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4. VIRAL TESTING REBOUND IN “REAL WORLD” DATABASE

The Sponsor investigated the feasibility of using real-time electronic health record data to identify PAXLOVID-prescribed patients who tested positive for COVID-19 after a negative test for COVID-19 using the Truveta U.S. Health Systems database. According to the sponsor, Truveta partners with 20 health systems, and data from 7 health systems contributed to this analysis. Truveta de-identifies billions of clinical data points and aggregates them daily in the Truveta Platform.

The research questions investigated included the following:

1. How often is testing for COVID-19 performed following a PAXLOVID prescription?
2. What are the COVID-19 testing result patterns following a PAXLOVID prescription?
3. How often does a patient who received PAXLOVID test negative for COVID-19 and later test positive?

There are several limitations to these analyses. The sponsor noted that data quality evaluation for this analysis is for feasibility studies only, and the reported data have not undergone full validation. Manual chart review to confirm accuracy was not performed and data quality assessments were performed ad hoc while authoring data extraction queries. Also, normalization of test result values/terminology is ongoing. The platform also captures medication orders and does not confirm patients filled the medication or took the medication as prescribed.

Also note that these analyses were focused on RT-PCR laboratory tests for SARS-CoV-2 that were administered by the member health system. There is no description about the actual site sampled for the RT-PCR assay. Also, laboratory tests administered outside the health system, including community-operated laboratories and at-home tests, may not be reconciled to the patient's medical record. Thus, patients who were tested outside the health system and did not have a healthcare contact that would result in a laboratory test reconciliation would be missing from this analysis. Home tests (e.g. rapid home antigen testing) are not included in these data.

Of the 46,389,076 patients identified in the Truveta Platform from 12/23/2021 to 5/6/2022, 6,281 patients were identified as receiving a prescription order for PAXLOVID. Of those 6,281 patients, only 49 received a test for COVID-19 within 6-27 days following their PAXLOVID prescription. Of the 49 patients tested, 26 patients tested positive and 23 tested negative for SARS-CoV-2 infection. After a negative COVID-19 test result, 0 patients later tested positive for COVID-19. It is unclear to this reviewer how many of the 23 subjects with a negative test even had a subsequent test conducted.

Overall, this reviewer does not find these analyses, which appear to be preliminary, as informative regarding the frequency or potential clinical relevance of viral RNA (or antigen or virus) rebound following PAXLOVID treatment in “real world” use.

5. CONCLUSIONS

- Based on analyses conducted both by the sponsor and independently by FDA, rebounds in SARS-CoV-2 RNA levels in NP/nasal swab samples were observed in a subset of subjects following treatment with either PAXLOVID or placebo in clinical trial C4671005 (EPIC-HR).
- The likelihood of detecting viral RNA rebound and the percentage of subjects having viral RNA rebound is impacted substantially by the definition, frequency of testing, and number of test results considered.
- In an FDA analysis using a definition which maximizes sensitivity to detect post-treatment viral RNA rebound, post-treatment (i.e., post-Day 5) viral RNA rebound was observed in 8.1% of PAXLOVID recipients and 5.4% of placebo recipients (p=0.02, Fisher's Exact Test).

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- Rates of post-treatment viral RNA rebound were confounded by the greater proportion of Day 5 virologic responders in the PAXLOVID group; post-treatment viral RNA rebound rates were not statistically different ($p>0.2$) between PAXLOVID and placebo recipients when analyses were restricted to Day 5 virologic responders.
- Rates of post-treatment viral RNA rebound were generally similar for PAXLOVID and placebo recipients across various other analysis timepoints and definitions.
- At each analysis timepoint, in both the treatment and post-treatment periods, a similar or greater percentage of PAXLOVID recipients had viral RNA <LLOQ compared to placebo recipients, regardless of any differences in viral RNA rebound rates.
- Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28.
- Post-treatment viral RNA rebound was not associated with immunosuppression risk or HIV-1 infection, although there were few such subjects for analysis ($n=14$; 13 immunosuppressed, 1 HIV-1).
- Post-treatment viral RNA rebound was not associated with PAXLOVID treatment-emergent resistance.
- In an analysis conducted by the sponsor, post-treatment viral RNA rebound was not associated with NIR plasma exposures.
- Based on another analysis conducted by the sponsor, post-treatment viral RNA rebound was not associated with recurrence of moderate-severe symptoms.
- Preliminary analyses of a “real-world” electronic health record database generally were not informative regarding the frequency and potential clinical relevance of viral rebound following PAXLOVID treatment.
- Additional resistance analyses are ongoing.

6. LIMITATIONS AND OTHER COMMENTS

- The analyses described in this review were primarily virology-centric analyses focused on SARS-CoV-2 RNA levels in NP swab samples.
- Viral RNA levels may vary in other upper respiratory tract sites, and in clinical practice, NP sampling is presumably less common. Non-NP sampling sites in the upper respiratory tract may be less sensitive for detection and quantification of SARS-CoV-2 RNA shedding.
- These analyses were not based on other body compartments that are important in viral pathogenesis, such as the lungs or other non-respiratory tissues. It should not be assumed that viral RNA levels in NP swabs are directly correlated with viral RNA levels in other body compartments.
- None of these analyses were based on SARS-CoV-2 antigen testing. Rapid antigen tests are commonly self-administered and are also less sensitive than RT-PCR analyses of NP swab samples.
- Measures of viral RNA or viral antigen do not necessarily reflect culturable virus or virus that is able to transmit to others. Viral RNA does not necessarily reflect fully replication competent virus, and a post-treatment increase in viral RNA level in NP samples by itself does not necessarily indicate a “relapse” in viral infection. The sponsor is in the process of assessing for the presence of cell culture infectious virus in NP swab samples from C4671005.
- Analyses of recurrence of mild symptoms in C4671005 have not yet been conducted or reported, although the review team has requested such analyses by the sponsor. These analyses are important

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to understand the clinical relevance of viral RNA rebound; however, they will likely be challenging due to a lack of objective, standardized measures for identifying and quantifying mild COVID-19 symptoms.

- Clinical trial C4671005 was conducted in an unvaccinated population, and ~99% of subjects enrolled in the trial with available viral sequencing data were infected with a SARS-CoV-2 Delta variant. Although nirmatrelvir has been shown to retain activity against other SARS-CoV-2 variants, including Omicron and various Omicron sub-lineages, it is unknown if the frequency or clinical relevance of post-treatment viral RNA rebound varies by vaccination status or infection with different SARS-CoV-2 variants.
- The sponsor plans to conduct a clinical trial, C4671042, to investigate further the clinical relevance of post-treatment viral RNA rebound and the potential benefit of PAXLOVID re-treatment in such cases (see also Clinical Virology review of [SDN 134](#)).
- In addition, the sponsor is planning another trial, C4671034, which will evaluate different durations of PAXLOVID treatment in immunocompromised patients with COVID-19. This trial may help to inform the potential benefit of a longer PAXLOVID treatment duration both in terms of clinical outcomes as well as the prevention of post-treatment viral rebound (see also Clinical Virology review [of IND 153517 SDNs 222/223](#)).

7. PROPOSED EDITS TO [PAXLOVID FACT SHEET FOR HEALTHCARE PROVIDERS](#)

Based on the analyses and conclusions from this review, we proposed including new text in the PAXLOVID EUA Fact Sheet for Healthcare Providers to summarize the post-treatment viral RNA rebound results from the EPIC-HR trial. The following text was added to Section 12.4 Microbiology and agreed upon between the sponsor and FDA. Note that we had originally proposed quoting specific rates of post-treatment viral RNA rebound based on 1 or 2 different analysis definitions, but the sponsor and FDA aligned on not quoting a specific rate due to the variability in viral RNA rebound rates according to different definitions, the anticipated variability in viral RNA rebound rates identified by different assays used in trials and clinical practice, and the potential for misinterpretation that the rates reflect symptomatic COVID-19 rebound, which was not measured in these analyses.

Final agreed upon language:

Viral RNA Rebound

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients, regardless of the rebound definition used. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by Mpro sequencing. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

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CONCURRENCES

Date: _____
DAV/Clin Virol TL/J O'Rear

cc: DAV/RPM/Moruf

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.

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