

**Emergency Use Authorization (EUA) for
Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets)
Center for Drug Evaluation and Research (CDER) Review**

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s) ¹	EUA 105
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	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)
Manufacturer, if different from Sponsor	
Submission Date(s)	October 21, 2021 November 11, 2021 Full EUA request- November 16, 2021
Receipt Date(s)	October 21, 2021 November 11, 2021 Full EUA request- November 16, 2021
OND Division / Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)/Discipline(s)	<ul style="list-style-type: none"> • ADL: Stacey Min • Clinical: Stephanie Troy/Sarah Connelly • Clin Virology: Pat Harrington/Jules O’Rear/Nonclinical Virology: Jonathon Rawson • Biometrics: Jie Cong/Thamban Valappil/Karen Higgins • Pharm/Tox: (Jenny) Zheng Li /Christopher Ellis • Clinical Pharmacology: Cristina Miglis, Ye Xiong, Jiang Liu, Mario Sampson, Vikram Arya • CMC ATL: David Claffey/ • Drug Substance: Katherine Windsor/Paresma Patel

¹ If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

	<ul style="list-style-type: none"> • Drug Product: DP: Shalini Anand/ David Claffey • Biopharm: Gerlie Gieser/ Elsbeth Chikhale • OPMA: Abdollah Koolivand Hang Guo/Derek Smith • OMQ: Tara Gooen and Diane Bruce • RBPM: Shamika Brooks • DMEPA: Melina Fanari/Sevan Kolejian • OSE: Rachna Kapoor/Kimberly Swank/Kate McCartan/Neha Gada/Natasha Pratt/Monique Falconer/Naomi Boston/Ida-Lina Diak/Mishale Mistry/Michael Blum/Attinello, Cristina/Danyal Chaudhry • PLT: • OPDP: Nima Ossareh/ Sam Skariah • CTECs: Brad Leissa, Liz Sadove, Andrea Gormley • OND Policy: Andrew Leboeuf • RPM: Alicia Moruf
Integrated Review Completion Date	12/22/2021
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	EUA for the emergency use of PAXLOVID for the 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
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	

I. **EUA Determination/Declaration**

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared, on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. **Recommendations**

A. **Recommend EUA Issuance**

The Division of Antivirals and Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA should authorize Paxlovid (nirmatrelvir co-administered with ritonavir) for emergency use as 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 risk² for progression to severe COVID 19, including hospitalization or death.

B. **Eligibility of the Product for an EUA**

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Nirmatrelvir (NIR), one of the components of Paxlovid, 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. Ritonavir (r), with which NIR is co-packaged in Paxlovid (NIR/r), is an HIV-1 protease inhibitor

² For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

and potent inhibitor of the CYP3A4 enzyme that increases the plasma levels of NIR for the desired therapeutic effect.

- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that Paxlovid may be effective 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. Under such conditions, the known and potential benefits outweigh the known and potential risks of this product.
- There is no adequate, approved, and available alternative to the emergency use of Paxlovid 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. Remdesivir (Veklury®), which is administered by intravenous infusion, is the only product approved by FDA to treat COVID-19 at the time of FDA's EUA review of Paxlovid. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed use under EUA

The Division recommends the following for inclusion in the EUA:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Paxlovid 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 risk³ for progression to severe COVID-19, including hospitalization or death.

Paxlovid is not approved for any use, including for use for the treatment of COVID-19.

Paxlovid is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of Paxlovid under section

³ For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.⁴
- Paxlovid is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- Paxlovid is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).⁵

Authorized Dosage(s) under EUA

Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg):

- Paxlovid, 300 mg NIR (two 150 mg tablets) co-packaged with 100 mg ritonavir (one 100 mg tablet), all three tablets taken together twice daily for 5 days, with or without food.
- The 5-day treatment course of Paxlovid should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient may complete the full 5-day treatment course per the healthcare provider's discretion.
- If the patient misses a dose of Paxlovid within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Patients with Renal Impairment

No dose adjustment is recommended in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) 60 to <90 mL/min].

In patients with moderate renal impairment (eGFR \geq 30 to <60 mL/min) the recommended dose is 150 mg NIR (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) all taken together twice daily for 5 days.

⁴ Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

⁵ The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min).

Patients with Hepatic Impairment

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

Pregnant or Lactating Women

No PK or safety data are available in pregnant or lactating women; the need for Paxlovid dose adjustment in pregnant or lactating women has not been established.

Geriatric Patients

No dosage adjustment is recommended in geriatric patients. Clinical trials of Paxlovid included patients 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. Of the total number of subjects in EPIC-HR randomized to receive Paxlovid (n=1,120), 13% (n=140) were 65 years of age and older and 3% (n=36) were 75 years of age and older.

Rationale for dosing regimen

- The proposed Paxlovid dosing regimen (300 mg NIR/100 mg ritonavir twice daily for 5 days) is primarily supported by the data from the EPIC-HR Study where it was generally safe and well-tolerated and may be effective at reducing the risk of COVID-19 related hospitalization or death from any cause through Day 28.
- This dosing regimen was the only regimen evaluated in EPIC-HR, which was the only Paxlovid study that evaluated the treatment of mild-to-moderate COVID-19 in symptomatic patients at high risk for progression to severe COVID-19.
- The dosing regimens for patients with renal or hepatic impairment were based on Phase 1 PK studies.
- The Paxlovid 300 mg NIR/100 mg ritonavir dose was initially chosen based on efficacy in the mouse model at concentrations approximating the in vitro EC90 (292 ng/mL) and simulations with a preliminary population PK model suggesting that greater than 90% of subjects achieve a trough concentration above the EC90 after the first dose. The 5-day treatment duration was based on the viral dynamics of SARS-CoV-2 in a quantitative systems pharmacology model.
- Paxlovid is recommended to be given without regard to food. A high fat meal did not significantly impact the AUC (AUC_{last} and AUC_{0-inf}) or C_{max} of NIR (approximately 15% increase in mean C_{max}, 1.5% increase in mean AUC_{last} and AUC_{0-inf}) following single dose administration of a 250 mg oral suspension in

healthy subjects. (See *Section XI, Human Clinical Pharmacology* for more information on food effect and early clinical NIR formulations). In the pivotal Phase 2/3 study, the final 150 mg tablet formulation was administered without regard to food.

IV. Product Information (Dose Preparation and Administration)

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate cavities within the same child-resistant blister card. Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

PAXLOVID is stored at Controlled Room Temperature 20°C to 25°C (68°F to 77°F).

Dispensing for patients with moderate renal impairment:

In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), the recommended dosage is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days, which is incongruent with how PAXLOVID is packaged. Consequently, to ensure that patients with moderate renal impairment take the correct dose, a Dear Health Care Provider letter and instructions for pharmacists (that will accompany each shipment of PAXLOVID) will outline the following risk mitigation steps:

- The healthcare provider should ensure that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:
 1. PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or
 2. PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment
- The pharmacist should make the following changes to all 5 blister cards and the carton for patients with moderate renal impairment:
 1. Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of each blister card (the removed tablets should be the ones closest to the middle of the blister pack).
 2. Affix each blister card with one sticker from the provided tear pad and apply it to cover the empty blister wells and to cover the pre-printed dosing instruction that is on the blister card.

3. Repeat steps one and two as described above for every blister card in the carton (each carton contains five blister cards).
 4. Affix one sticker from the provided tear pad and carefully apply it to cover over the pre-printed dosing regimen on the carton.
- The pharmacist should counsel patients with moderate renal impairment about renal dosing instructions and notify them that their blister cards have been altered by the pharmacy.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on the Condition

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named COVID-19. COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 271 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of December 17, 2021, including an estimated 5.3 million deaths. As of December 17, 2021, approximately 51 million cases of COVID-19, including approximately 803,000 deaths, have been reported in the United States according to CDC.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report, in early January 2021 <10% of SARS-CoV-2 variants circulating in the US were variants of concern or interest. However, by the end of March 2021, approximately two-thirds of SARS-CoV-2 variants circulating in the US were variants of concern or interest, with B.1.1.7 (Alpha) comprising 44% of circulating variants at the time. B.1.1.7 was supplanted as the most prevalent variant in the US in June 2021 by the Delta variant (B.1.617.2 and AY lineages), which accounted for 97% of circulating SARS-CoV-2 in the US, as well as most SARS-CoV-2 globally, by August 2021. In November 2021, the Omicron (B.1.1.529) variant was detected in South Africa and has spread globally; characteristics of this variant, including its susceptibility to currently authorized treatments, are still being discovered.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations, with disease severity ranging from mild to severe/critical illness⁶. Severe/critical illness is defined as hospitalization, admission to the intensive care unit, mechanical ventilation, or death. The progression of SARS-CoV-2 infection to severe or critical COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, over 80% of

⁶ The different severities of COVID-19 illness are described in the NIH COVID-19 Treatment Guidelines at <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>.

COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy, and immunocompromised states, increase the risk of progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as many racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Göttinger et al., 2020).

Treatment Alternatives

There is no adequate, approved, and available alternative to the emergency use of Paxlovid 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.

Remdesivir (Veklury®) is the only product approved by FDA to treat COVID-19 at the time of FDA's EUA review of Paxlovid. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir initially received emergency use authorization on May 1, 2020, and was ultimately approved on October 22, 2020, under NDA 214787. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization. At the time of this review, remdesivir also remains authorized for emergency use for treating suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

There are other COVID-19 treatments currently authorized for emergency use for the same use as proposed for Paxlovid: 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. These products include the following:

1. REGEN-COV (the monoclonal antibodies casirivimab and imdevimab) was authorized on November 21, 2020.
2. The monoclonal antibodies bamlanivimab and etesevimab were authorized to be administered together on February 9, 2021.
3. The monoclonal antibody sotrovimab was authorized on May 26, 2021.

There are currently no approved therapies for treatment of mild-to-moderate COVID-19 in outpatients. Additional information on COVID-19 treatments can be found at <https://www.cdc.gov/coronavirus/2019-ncov/index.html>.

VI. Related Regulatory Submission(s)

Paxlovid (NIR co-packaged with ritonavir) has been studied under IND 153517 (Sponsor: Pfizer Inc.).

Product quality information supporting ritonavir tablets were referenced to (b) (4) (ritonavir) tablets).

Pfizer proposed two suppliers for blister packaging components:

- DMF (b) (4)
- DMF (b) (4)

Both DMF (b) (4) were found adequate to support this application.

VII. Summary of Clinical Data

The data to support the authorization of Paxlovid were generated from the ongoing Phase 2/3 trial EPIC-HR. Additional data from five Phase 1 studies also support the authorization (Table 1).

Paxlovid is also being studied in two ongoing Phase 2/3 trials. However, data from these trials were not submitted to support this EUA application.

1. Five days of Paxlovid (300 mg NIR and 100 mg ritonavir po bid) is being studied in EPIC-SR (C4671002), a Phase 2/3 COVID-19 treatment trial in 1140 non-hospitalized adults at low risk for severe disease.
2. Five days versus 10 days of Paxlovid (300 mg NIR and 100 mg ritonavir po bid) is being studied in EPIC-PEP (C4671006), a Phase 2/3 COVID-19 post-exposure prophylaxis trial in 2,660 asymptomatic, SARS-CoV-2 negative adult household contacts of individuals infected with SARS-CoV-2.

Table 1: Clinical Trials with Data Submitted to Support this EUA Application

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
EPIC-HR (C4671005) NCT04960202	IND 153517	Efficacy, safety, PK	2,246* adult outpatients with COVID-19 at high risk for severe disease	Phase 2/3 randomized (1:1), double-blind, placebo-controlled trial	Nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 days versus placebo	Ongoing but enrollment complete
C4671001 NCT04756531	IND 153517	PK, safety	70 healthy adults	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose, multiple ascending dose study	Single doses: nirmatrelvir 150, 250, 500, or 1500 mg or nirmatrelvir 250, 300, 750, or 2250 mg with ritonavir 100 mg at -12, 0, and 12 hours Multiple doses: nirmatrelvir 75, 250, or 500 mg bid with 100 mg ritonavir bid x 10 days	Completed
C4671010 NCT05005312	IND 153517	PK, safety	Adults with moderate hepatic impairment (n=8) or normal hepatic function (n=8)	Phase 1, open-label study	Nirmatrelvir 100 mg po x1 with ritonavir 100 mg at -12, 0, 12, and 24 hours	Ongoing; topline data only [^]
C4671011 NCT04909853	IND 153517	PK, safety	34 adults with renal impairment or normal renal function	Phase 1, open-label study	Nirmatrelvir 100 mg po x1 with ritonavir 100 mg at -12, 0, 12, and 24 hours	Completed
C4671014 NCT04962230	IND 153517	PK, safety	12 healthy adults	Phase 1, open-label, fixed sequence, 2-period crossover study	Period 1: single dose of nirmatrelvir 300 mg and ritonavir 100 mg Period 2: carbamazepine 100 mg bid Days 1-3, 200 mg bid Days 4-7, and 300 mg bid Days 8-15 with a single dose of nirmatrelvir 300 mg and ritonavir 100 mg on Day 13	Completed
C4671015 NCT04962022	IND 153517	PK, safety	12 healthy adults	Phase 1, open-label, fixed sequence, 2-period crossover study	Period 1: nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 doses Period 2: itraconazole 200 mg qd x 8 days with nirmatrelvir 300 mg and ritonavir 100 mg po bid x 5 doses starting on Day 4	Completed

IND = investigational new drug application, PK = Pharmacokinetics, po = orally, bid = twice a day, qd = daily

*The initial EUA application contained an interim analysis based on data from 1349 subjects, but topline efficacy and safety data from all 2246 subjects enrolled in C4671005 was provided before the end of the review (submitted 12/14/2021).

[^]A topline summary of preliminary unaudited data for this study was submitted midway through the review cycle.

Sources: EUA request Table 7, the individual study protocols, and clinicaltrials.gov (for the NCT numbers).

VIII. Human Clinical Efficacy

The main source of clinical efficacy data to support this EUA request was from the Phase 2/3 study C4671005 (EPIC-HR, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04960202) identifier NCT04960202).

EPIC-HR (C4671005) Trial Design

EPIC-HR is a Phase 2/3, randomized, double-blind, placebo-controlled trial of Paxlovid for the treatment of adult outpatients with mild-to-moderate COVID-19, who are at high-risk for progression to severe disease. Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within five days were randomized 1:1 to receive Paxlovid (NIR 300 mg coadministered with ritonavir 100 mg) or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and whether subjects had received or were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization. The total study duration is up to 24 weeks.

Inclusion/exclusion criteria specified that subjects had to have at least one of the following risk factors for progression to severe disease: ≥ 60 years of age; BMI > 25 ; current smoker; immunosuppressive disease or immunosuppressive treatment; chronic lung disease; hypertension; cardiovascular disease; diabetes; chronic kidney disease; sickle cell disease; neurodevelopmental disorders; active cancer; medical related technological dependence. Individuals who had a history of prior COVID-19 infection or vaccine were excluded.

Enrollment of subjects who had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25% of subjects. 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 subjects.

An independent external data monitoring committee (E-DMC) reviewed unblinded safety data on an ongoing basis throughout the duration of the study, 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 mITT analysis set 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 set completed the Day 28 assessments.

The primary analysis set was updated to include only those ≤ 3 days of COVID-19 symptom onset in protocol amendment 2 (8/2/2021) and the total sample size was increased from 2260 to approximately 3000. Sites in India were terminated (on 9/22/2021) due to a blinded data review of a $> 90\%$ rate of serology positive

subjects at baseline and Site 1470 was terminated for GCP noncompliance (refer to *Efficacy Results* for sensitivity analysis). 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 of 10/26/2021) and further enrollment in the study was subsequently stopped on 11/5/2021. The final efficacy analysis was conducted as a supportive analysis after all subjects completed the Day 34 visit. The follow-up analysis will be performed after all subjects have completed the Week 24 visit.

Analysis Populations

The Full Analysis Set (FAS) included all subjects randomly assigned to study intervention regardless of whether or not study intervention was administered. The following analysis populations were used for efficacy analyses.

- 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.

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

Efficacy Results

The EUA submission originally included EPIC-HR interim analysis efficacy data; later in the EUA review cycle on 12/14/2021 topline efficacy analyses on final data were submitted. Therefore, the following two subsections provide the interim analysis efficacy results along with the later submitted full topline analysis efficacy results.

Interim Analysis Efficacy Results

As of the data cutoff (10/26/2021), 1,361 subjects were included in the full analysis set in the interim analysis. The table below displays demographic and baseline characteristics.

Table 2: Baseline Demographics and Disease Characteristics (FAS), Interim Analysis

	Paxlovid n=678	Placebo n=683
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Female	334 (49%)	314 (46%)
Hispanic or Latino	324 (48%)	330 (48%)
Black or African American	37 (5%)	25 (4%)
Asian	134 (20%)	140 (20%)
Age (median years)	42.0	45.0
Age ≥ 60 years	109 (16%)	146 (21%)
BMI (mean kg/m ²)	29.1	29.2
BMI ≥ 30 kg/m ²	246 (36%)	253 (37%)
Duration of COVID-19 symptoms ≤ 3 days	433 (64%)	426 (62%)
Viral Load (NP samples, mean, log ₁₀ copies/mL)	4.69	4.72
Viral Load ≥ 10 ⁷ (units) ^a	171 (27%)	166 (26%)
Seropositive ^b	372 (56%)	368 (55%)
United States	304 (45%)	304 (45%)
COVID-19 mAb treatment received/expected to receive	55 (8%)	57 (8%)

Sources: EUA request Table 36

^a Denominator being participants with available baseline viral load

^b Denominator being participants with available baseline serology status

Clinical Outcomes

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 and without COVID-19 therapeutic mAb treatment at baseline. The event rates were 27/387 (7.0%) in the placebo group, and 3/393 (0.8%) in the Paxlovid group. 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.

Table 3: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT), Interim Analysis

	Paxlovid n=393	Placebo n=387
Subjects 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) ^a	-6.3% (-9.0%, -3.6%)	
p-value	<.0001	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 2

^a 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.

Consistent results were shown in sensitivity analyses of the primary efficacy endpoint where data from India and Site 1470 were excluded and where subjects who received a therapeutic COVID-19 mAb treatment postbaseline were considered to have experienced a primary endpoint event.

Additionally, in a sensitivity analysis on the primary efficacy endpoint where subjects who had unknown hospitalization/death status through Day 21 were imputed to have experienced an event of COVID-19-related hospitalization or death, the result favored treatment with Paxlovid with a p-value 0.0039 in the mITT analysis set for the interim analysis data, and a finding consistent with the interim analysis (Table 3) was obtained in the mITT analysis set for the full topline data.

Treatment with Paxlovid showed no inconsistent effect in subgroup analyses of age, gender, race, BMI, baseline serology status, baseline viral RNA in NP samples, baseline comorbidities, and geographic region.

The first key secondary endpoint was the proportion of subjects with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set, who received treatment within 5 days of symptom onset and without COVID-19 therapeutic mAb treatment at baseline. The event rates were 41/620 (6.6%) in the placebo group, and 6/617 (1.0%) in the Paxlovid group. Treatment with Paxlovid showed a 5.7% (95% CI: -7.9% to -3.6%) absolute reduction, or 85.3% relative reduction compared to placebo.

Table 4: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT1), Interim Analysis

	Paxlovid n=617	Placebo n=620
Subjects 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) ^a	-5.7% (-7.9%, -3.6%)	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 3

^a 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.

A sensitivity analysis was conducted in the mITT2 analysis set who received treatment regardless of baseline COVID-19 therapeutic mAb treatment. The event rates were 43/677 (6.4%) in the placebo group, and 7/672 (1.0%) in the Paxlovid group. Treatment with Paxlovid showed a 5.4% (95% CI: -7.4% to -3.4%) absolute reduction, or 83.6% relative reduction compared to placebo.

Table 5: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT2), Interim Analysis

	Paxlovid n=672	Placebo n=677
Subjects 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) ^a	-5.4% (-7.4%, -3.4%)	

Sources: Response to 06 December 2021 and 07 December 2021 Information Request, Table 1

^a 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.

Full Topline Analysis Efficacy Results

The full topline analysis findings were submitted on December 14, 2021; the Agency determined that these findings were important to consider for the EUA request. A total of 2,246 subjects were randomized into this study. The table below displays demographic and baseline characteristics.

Table 6: Baseline Demographics and Disease Characteristics (FAS), Full Topline Analysis

	Paxlovid n=1,120	Placebo n=1,126
Female	554 (49%)	544 (48%)
Hispanic or Latino	499 (45%)	505 (45%)
Black or African American	60 (5%)	50 (4%)
Asian	154 (14%)	161 (14%)
Age (median years)	45.0	46.5
Age ≥ 60 years	226 (20%)	260 (23%)
BMI (mean kg/m ²)	29.1	29.3
BMI ≥ 30 kg/m ²	407 (36%)	419 (37%)
Duration of COVID-19 symptoms ≤ 3 days	754 (67%)	735 (65%)
Viral Load (NP samples, mean, log ₁₀ copies/mL)	4.67	4.59
Viral Load ≥ 10 ^{^7} (units) ^a	300 (27%)	275 (24%)
Seropositive ^b	581 (52%)	568 (50%)
United States	463 (41%)	465 (41%)
COVID-19 mAb treatment received/expected to receive	70 (6%)	70 (6%)

Sources: Preliminary Completion Date Summary Report Study C4671005, Table 4

^a Denominator being participants with available baseline viral load

^b Denominator being participants with available baseline serology status

Clinical Outcomes

Using the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 endpoint, Paxlovid showed an 88.9%, 87.8%, and 86.7% relative risk reduction compared to placebo in the mITT, mITT1, and mITT2 analysis sets, respectively. These results supported the efficacy conclusion from the interim analysis.

Table 7: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, Full Topline Analysis

<i>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</i>		
	Paxlovid n=697	Placebo n=682
Subjects with event, n (%)	5 (0.7%)	44 (6.5%)
COVID-19 hospitalization	5 (0.7%)	44 (6.5%)
Death	0	9 (1.3%)
Estimated difference in proportion (95% CI) ^a	-5.8% (-7.8%, -3.8%)	
<i>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 expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset</i>		
	Paxlovid n=1,039	Placebo n=1,046
Subjects with event, n (%)	8 (0.8%)	66 (6.3%)
COVID-19 hospitalization	8 (0.8%)	65 (6.2%)
Death	0	12 (1.1%)
Estimated difference in proportion (95% CI) ^{a, b}	-5.6% (-7.2%, -4.0%)	
<i>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</i>		
	Paxlovid n=1,109	Placebo n=1,115
Subjects with event, n (%)	9 (0.8%)	68 (6.1%)
COVID-19 hospitalization	9 (0.8%)	67 (6.0%)
Death	0	12 (1.1%)
Estimated difference in proportion (95% CI) ^a	-5.4% (-6.9%, -3.8%)	

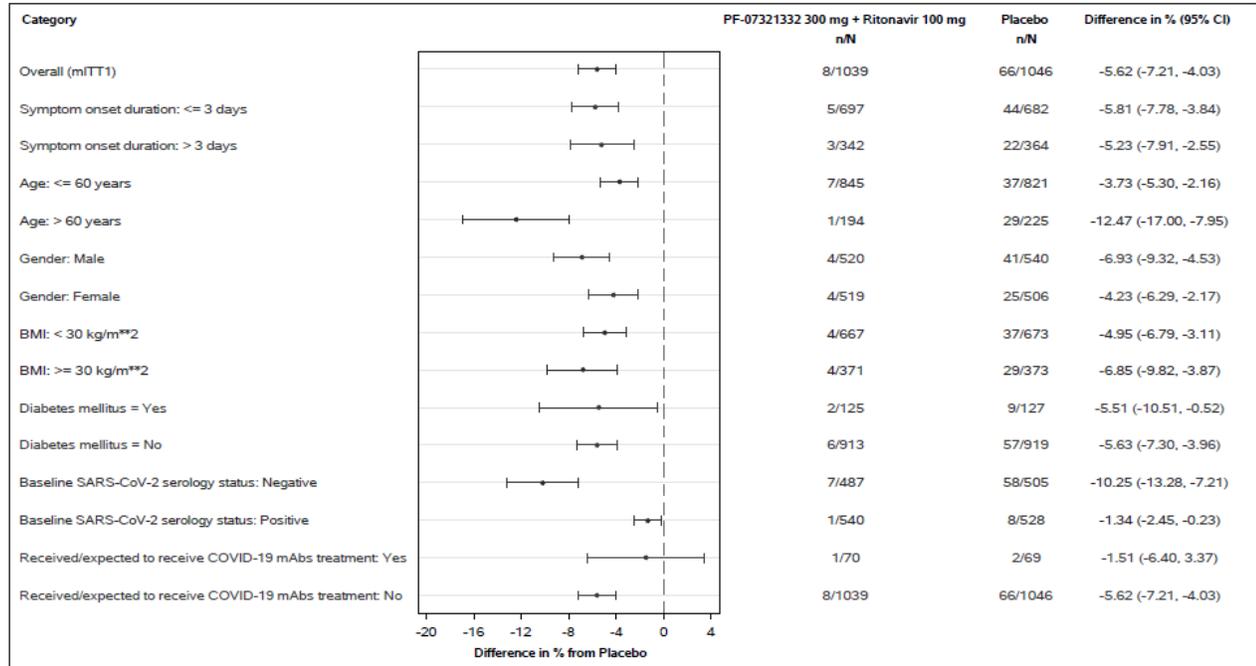
Sources: Preliminary Completion Date Summary Report Study C4671005, Table 5, Table 6, Table 7

^a 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

^b The relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%)

Subgroup analyses were conducted in the mITT1 analysis set by symptom onset duration (≤ 3 days or not), age group (≤ 60 or not), gender, BMI (< 30 or not), diabetes mellitus, baseline serology status, and in the mITT2 analysis set by mAb use status (at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment). Treatment with Paxlovid showed no inconsistent effect in any subgroup of subjects.

Figure 1: Proportion of Subjects with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 (mITT1), Full Topline Analysis



Sources: Response to FDA Information Request, submitted 12/16/2021

Virologic Outcomes

The statistical analysis of viral RNA levels in NP swabs first occurred when approximately 200 subjects in the mITT analysis set completed the viral RNA shedding assessment at Day 5 and had valid viral RNA measurements at both Day 1 and Day 5 available for an initial proof-of-concept (POC) assessment. Only samples collected with the validated I-Swab-plus were used for formal viral RNA analysis. Subjects were excluded from the analysis due to missing or baseline viral RNA was not detected, or collection with a unvalidated (local) swab. Data reported as less than 2.0 log₁₀ copies/mL were recorded as 1.69 log₁₀ copies/mL and data reported as “not detected” were recorded as 0 log₁₀ copies/mL. A snapshot of the database took place on 9/20/2021 and the POC assessment included all subjects who had data in the database at the time.

In the mITT1 analysis set, baseline viral RNA levels averaged 5.11 log₁₀ copies/mL among the 303 subjects in the placebo group, and 5.41 log₁₀ copies/mL among the 269 subjects in the Paxlovid group. At Day 5, after accounting for baseline viral RNA level, geographic region, serology status and symptom onset, the adjusted mean (SE) reduction in viral RNA level was -1.75 (0.09) log₁₀ copies/mL in the placebo group, and -2.69 (0.10) log₁₀ copies/mL in the Paxlovid group, reflecting an additional average reduction (SE) of -0.93 (0.13) log₁₀ copies/mL. The adjusted mean reductions in viral RNA from baseline to Day 5 in the mITT and mITT2 analysis sets were comparable to that for the mITT1 analysis set.

During the review the sponsor provided an analysis-ready dataset of available viral RNA results from subjects in EPIC-HR. Independent FDA analyses were conducted on 852 subjects (424 Paxlovid treated, 428 Placebo treated) who had available NP swab viral RNA data, at minimum, on both Day 1 (Baseline) and Day 5 (EOT). Note that this is a larger sample size than that presented in the sponsor's initial analyses of viral RNA shedding.

Overall results of viral RNA levels in NP swabs are summarized in Table 8, and were consistent with the sponsor's POC analyses summarized above. Treatment with Paxlovid was associated with a ~0.9 log₁₀ copies/mL greater median reduction in SARS-CoV-2 RNA levels in NP swabs through Day 5 (EOT). Similar trends indicating modestly greater SARS-CoV-2 RNA declines in Paxlovid treated subjects were observed across different key subgroups, including the mITT, mITT1 and mITT2 populations. In these analyses similar declines in viral RNA levels were observed in anti-SARS-CoV-2 seronegative and seropositive subjects.

Table 8. Viral RNA changes (log₁₀ copies/mL) from Baseline in NP swab samples (mITT2 population, all subjects with available data at Baseline and Day 5).

Analysis Visit	Placebo			Paxlovid		
	N	Mean	Median	N	Mean	Median
Baseline	428			424		
Day 3	400	-1.2	-1.3	397	-1.7	-1.7
Day 5	428	-2.1	-2.0	424	-2.9	-2.9
Day 10	325	-3.9	-4.0	328	-4.2	-4.4
Day 14	336	-4.5	-4.7	330	-4.7	-5.0

Source: FDA analysis.

Resistance Analyses

The sponsor analyzed and submitted viral NGS analysis data from 490 subjects enrolled in EPIC-HR, of whom 216 (16% of mITT2 45% IA population) had sequence data available at both Day 1 and Day 5 (EOT) timepoints. Independent FDA analyses of the sponsor's analysis-ready amino acid frequency tables were conducted, focusing on treatment-emergent amino acid changes encoded in the Mpro (nsp5/3Clpro) gene as well as the 11 different Mpro cleavage sites (Table 9).

A large number of frameshift changes were detected at low amino acid frequencies (90% at ~6% or less frequency), which we interpreted to be predominantly sequencing artifacts, and thus we set our analysis sensitivity threshold at 5%. Given the limited available data for review, these analyses of NIR/r treatment-emergent substitutions should be considered preliminary.

Table 9. Mpro cleavage sites in SARS-CoV-2 open-reading frame 1ab (ORF1ab).

Cleavage Site	Proteins	Cleavage Sites	ORF1ab AA positions
Mpro Cleavage Site #1	nsp4/nsp5	SAVLQ↓SGFRK	3259-3268
Mpro Cleavage Site #2	nsp5/nsp6	GVTFQ↓SAVKR	3565-3574
Mpro Cleavage Site #3	nsp6/nsp7	VATVQ↓SKMSD	3855-3864
Mpro Cleavage Site #4	nsp7/nsp8	RATLQ↓AIASE	3938-3947
Mpro Cleavage Site #5	nsp8/nsp9	AVKLQ↓NNELS	4136-4145
Mpro Cleavage Site #6	nsp9/nsp10	TVRLQ↓AGNAT	4249-4258
Mpro Cleavage Site #7	nsp10/nsp11-12	EPMLQ↓SADAQ	4388-4397
Mpro Cleavage Site #8	nsp12/nsp13	HTVLQ↓AVGAC	5320-5329
Mpro Cleavage Site #9	nsp13/nsp14	VATLQ↓AENVT	5921-5930
Mpro Cleavage Site #10	nsp14/nsp15	FTRLQ↓SLENV	6448-6457
Mpro Cleavage Site #11	nsp15/nsp16	YPKLQ↓SSQAW	6794-6803

Source: adapted from [interim viral sequencing report](#), p. 5; report [PF-07321332 19Jan21 120222](#), p.17).

Treatment-emergent amino acid substitutions in Mpro or any Mpro cleavage sites detected at the same position in ≥2 Paxlovid treated subjects are summarized in Table 10. These substitutions included D153Y, Q189K and A260T/V in Mpro, and T6449I in Mpro cleavage site #10.

Table 10. Treatment-emergent amino acid substitutions in Mpro or Mpro cleavage sites detected at the same position in ≥2 Paxlovid treated subjects (C4671005 preliminary resistance analyses).

Substitution	In/Near (4Å) NIR Binding Site?	Number of Subjects with Tx-Emergent Substitution	
		Paxlovid (n=97)	Placebo (n=119)
Mpro_D153Y	No	2	0
Mpro_Q189K	Yes	5	7
Mpro_A260T/V	No	1(T), 3(V)	0
Mpro cl.site #10_T6449I	n/a	2	0

Source: FDA analysis.

Mpro_A260T/V appeared to have the strongest signal as possible Paxlovid treatment-emergent substitutions. The A260T substitution emerged in one Paxlovid treated subject at a variant frequency of 11%, and the A260V substitution emerged in 3 other subjects at a variant frequency of 6-21%; neither emerged in any placebo treated subjects. Nevertheless, the potential impact of either substitution on NIR resistance is unclear. This position is variable across different

CoVs, and within the dataset baseline polymorphisms [V (n=6), T (n=3) G (n=1) or P (n=1); 1-100% frequency] were detected at this position in 11/480 (2%) subjects in the dataset, none of whom reached the clinical endpoint of hospitalization or death. In a biochemical assay with recombinant Mpro expressing A260V, no reduction in NIR susceptibility was observed. This position should be closely monitored as more resistance data are obtained from the trial.

The Mpro_Q189K substitution emerged in 5 Paxlovid- and 7 placebo-treated subjects. This substitution is notable as Q189 is highly conserved and within 4Å of the NIR binding site in Mpro, and in a biochemical assay this specific substitution conferred a 65-fold reduction in NIR activity. However, based on further analyses it is unclear if Q189K was truly a Paxlovid treatment-emergent substitution in this preliminary dataset. There is no indication Q189K was enriched in Paxlovid-treated subjects relative to placebo-treated subjects. In both Paxlovid and placebo-treated subjects, Q189K was detected at Day 5 at a frequency of 5-10%, with the two highest frequencies (~10%) observed in placebo-treated subjects. Furthermore, there is strong evidence that Q189K was a commonly observed sequencing artifact. The sponsor noted the nucleotide sequence is in an AT-rich region, and despite Q189 being highly conserved in published SARS-CoV-2 sequence data, it was detected in 53% of subjects' baseline viral sequences in the current dataset, predominantly at a <5% frequency. Therefore, considering the totality of this information, FDA currently does not consider Q189K to be a known Paxlovid treatment-emergent substitution in treated patients, but this position should also continue to be monitored closely for possible clinical evidence of Paxlovid resistance.

The Mpro_D153Y substitution emerged in 2 Paxlovid treated subjects. In both cases the substitutions were detected at a ~6% frequency, near the sensitivity cutoff used in the assay. Therefore, it is unlikely this change reflects a true treatment-emergent resistance-associated substitution, but it is noted here for future reference.

The Mpro cleavage site #10_T6449I substitution also emerged in 2 Paxlovid treated subjects and were the predominant variants at this position on Day 5 in both subjects. We currently do not view this finding as indicative of NIR resistance emergence. Given there are 11 different Mpro cleavage sites, presumably changes would need to occur either in one critical site or in multiple different cleavage sites in the same virus to confer some level of NIR resistance, and this is the only cleavage site amino acid change that was detected in ≥2 Paxlovid treated subjects. Neither subject had any amino acid changes detected in Mpro at Baseline or Day 5.

SARS-CoV-2 RNA shedding results were analyzed to further investigate any association between potential NIR resistance-associated substitutions and virologic outcomes, although conclusions cannot be drawn from these analyses due to the limited available sequence analysis data. Of the 97 Paxlovid treated

subjects with available resistance data on Day 1 (Baseline) and Day 5, only 17 (18%) subjects had a substitution detected at either Day 1 or Day 5 at any possible resistance-associated amino acid position, defined loosely based on the totality of nonclinical and clinical resistance data analyzed to date (Table 11).

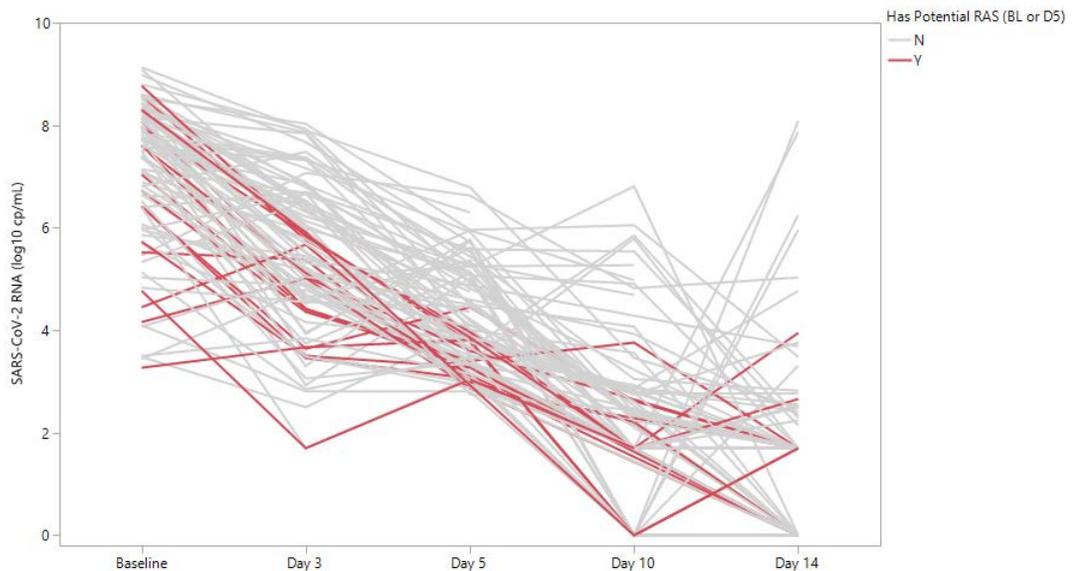
Table 11. Paxlovid treated subjects with SARS-CoV-2 amino acid substitutions in Mpro or cleavage site positions potentially associated with resistance (C4671005 preliminary resistance analyses).

Position	Possible Association w/NIR Resistance	Total # Changes (NIR/r)
G15	P15A possible minor MHV resistant-emergent change, G15S 4.4-fold change in biochemical assay	0
H41	within 5 Å of NIR	0
M49	within 5 Å of NIR	0
L50	T50K possible minor MHV resistant-emergent change	0
Y54	within 5 Å of NIR, Y54H 24-fold change in biochemical assay	0
E55	P55L emergent in resistant MHV	0
A129	T129M possible minor MHV resistant-emergent change	1 (Day 5, A129P)
T135	T135I 3.5-fold change in biochemical assay	0
F140	within 5 Å of NIR, F140A 39-fold change in biochemical assay	0
L141	within 5 Å of NIR	1 (Day 5, L141F)
N142	within 5 Å of NIR	0
G143	within 5 Å of NIR	0
S144	within 5 Å of NIR, S144A emergent in resistant MHV, 92-fold change in biochemical assay	1 (Day 5, S144P)
C145	within 5 Å of NIR	1 (Day 5, C145F)
D153	Position where tx-emergent substitutions were detected in C4671005	2 (Day 5, D153Y)
H163	within 5 Å of NIR	0
H164	within 5 Å of NIR, H164N 6.4-fold change in biochemical assay	0
M165	within 5 Å of NIR	0
E166	within 5 Å of NIR, E166A 33-fold change in biochemical assay	0
L167	within 5 Å of NIR	0
P168	within 5 Å of NIR	0
H172	within 5 Å of NIR, H172Y 233-fold change in biochemical assay	0
V186	within 5 Å of NIR	0
D187	within 5 Å of NIR	0
R188	within 5 Å of NIR	1 (Day 5, R188M)
Q189	within 5 Å of NIR, Q189K 65-fold change in biochemical assay, high freq. of suspected sequence artifacts in C4671005	6 (Q189K: 1 @ Day 1, 5 @ Day 5)
T190	within 5 Å of NIR	1 (Day 5, T190I)
A191	within 5 Å of NIR	0
Q192	within 5 Å of NIR	0
D248	D248E 3.7-fold change in biochemical assay	0
A260	Position where tx-emergent substitutions were detected in C4671005	4 (Day 5, 3 A260V, 1 A260T)
cleavage site #10 T6449	Position where tx-emergent substitutions were detected in C4671005	2 (Day 5, T6449I)
Detected at any timepoint (Baseline or Day 5) in 17/97 (18%) NIR/r treated subjects in C4671005 w/ resistance data (1 hospitalized)		

Source: FDA analysis.

SARS-CoV-2 RNA changes in NP swab samples generally did not differ substantially between Paxlovid treated subjects with or without any of the above-noted potential resistance-associated amino acid substitutions (Figure 2). Several subjects appeared to have a rebound in SARS-CoV-2 RNA levels around Day 10

or Day 14, although this occurred among subjects with or without potential resistance-associated substitutions detected at Day 1 or Day 5.



Source: FDA analysis.

Figure 2. SARS-CoV-2 RNA levels in NP swabs among Paxlovid treated subjects with or without SARS-CoV-2 amino acid substitutions detected in Mpro or cleavage site positions potentially associated with resistance.

In summary, currently there are no clear signals of baseline or treatment-emergent NIR resistance from the preliminary analyses of clinical trial EPIC-HR. These analyses will continue to be conducted as more complete data from EPIC-HR are obtained and reported.

IX. Human Clinical Safety

Paxlovid (NIR coadministered with ritonavir) is currently being evaluated in clinical trials for COVID-19 treatment in outpatient settings and for post-exposure prophylaxis against COVID-19 in asymptomatic household contacts of individuals with confirmed SARS-CoV-2 infection. For the proposed EUA, the safety database consists of data from EPIC-HR from 1109 adult non-hospitalized subjects with COVID-19 at high risk for severe COVID-19 who were randomized to receive Paxlovid po bid x 5 days and had follow-up data through Day 28 after initiating treatment.

- The EUA submission originally included EPIC-HR interim analysis safety data from 672 adults as well as topline preliminary safety data from an

additional 273 subjects who were randomized to receive Paxlovid in EPIC-HR and had not completed 28 days of follow-up.

- Later in the EUA review cycle on 12/16/2021 topline analysis safety data were submitted for the full safety analysis set.
- Supplemental data were also available from 7 healthy adult subjects who received Paxlovid at or above the proposed dose for at least 5 days in the Phase 1 study C4671001 (500 mg NIR with 100 mg ritonavir bid for 10 days).

In this EUA review, safety subsections provide the interim analysis safety assessment as the primary safety assessment followed by the later submitted full topline analysis safety assessment.

The safety population from EPIC-HR is most similar to the intended population for the proposed use under EUA of the currently ongoing Phase 2/3 trials in that these subjects have mild-to-moderate COVID-19 and are at high risk for severe disease. Key differences with the intended population for use under EUA include the following:

- Adolescents 12 years of age and older and weighing at least 40 kg were not included in the trials (the safety database only includes adults).
- Pregnant women were not included in the trials.
- Individuals with moderate to severe renal impairment, GFR <45 mL/min/1.73/m², history of active liver disease, or abnormal liver enzymes (AST or ALT ≥ 2.5 X upper limit of normal [ULN] or total bilirubin ≥ 2 X ULN) were excluded from EPIC-HR. However, separate renal impairment and hepatic impairment studies were conducted using single doses of 100 mg NIR administered with ritonavir (see Table 1).
- Individuals who received a COVID-19 vaccine were excluded from EPIC-HR and will not be excluded from the proposed EUA population (though it would be unlikely that prior COVID-19 vaccination would impact the safety profile of Paxlovid).
- A low percentage of subjects in EPIC-HR were black or African American (approximately 5%), and only one subject with HIV infection was enrolled.

EPIC-HR Safety Results

The safety analysis from the pivotal trial, EPIC-HR, includes 1109 Paxlovid recipients and 1115 placebo recipients with TEAEs reported up to Day 34.

- The initial EUA submission contained datasets and analysis for the interim analysis, which included 672 Paxlovid recipients and 677 placebo recipients with TEAEs reported up to Day 34 through the data cutoff date of October 26, 2021; these numbers differed from the numbers in the full analysis set because 12 subjects were not treated, and differed from the numbers in the mITT2 analysis set because 19 subjects were excluded from the mITT2 because they did not have at least one post-baseline visit through Day 28.

- Topline preliminary data for all enrolled subjects (including an extra 437 Paxlovid recipients and 438 placebo recipients) was submitted near the end of the review on 12/14/2021.

Adverse events in EPIC-HR were graded according to a five point scale adapted from the toxicity grading scale of the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1 (July 2017) from the National Institutes of Health. Clinical events related to COVID-19, including deaths and SAEs, could be included as AEs.

The primary safety analysis from the pivotal trial had the following major limitations (in addition to the limitations related to the population for the safety database listed previously):

1. The analysis of adverse events of special interest (hemodynamic events, inflammatory events, and thyroid related events) was not included in this submission, although data on AEs, vital signs, and laboratory markers were included.
2. In the interim analysis (with topline data suggesting similar proportions among all enrolled subjects), approximately one-third of subjects reported at least one important protocol deviation (in the full analysis set, 37% of Paxlovid recipients and 37% of placebo recipients). However, similar proportions of subjects had protocol deviations in each treatment group. In addition, the only two protocol deviations reported in >5% of subjects were ones that could negatively impact the efficacy assessment but should not affect the safety assessment: NIR or placebo and ritonavir or placebo taken >5 minutes apart (11% of subjects) and missing more than 25% of COVID-19-related symptoms diary entries (19% of subjects).

Safety Overview

Table 12 below shows the summary of safety events based on the EPIC-HR interim analysis. In general, rates of overall safety events were similar between treatment groups or higher in the placebo group, with the exception of AEs considered related to treatment. Similar results were observed in the topline safety results from all enrolled subjects.

Table 12: Summary of Overall Adverse Events in EPIC-HR through Day 34, Interim Analysis

	Paxlovid n=672	Placebo n=677
Any AE	133 (20%)	151 (22%)
AE related to study treatment	49 (7%)	29 (4%)
Any Grade 3 or higher AE	21 (3%)	58 (9%)
Any Grade 3 or higher AE related to study treatment	3 (<1%)	4 (<1%)
SAE	13 (2%)	46 (7%)
SAE related to study treatment	1 (<1%)	0

AEs with outcome of death	0	10 (1%)
Fatal AEs related to study treatment	0	0
AEs leading to discontinuation of study drug	16 (2%)	29 (4%)
AEs leading to discontinuation of study drug related to study treatment	7 (1%)	3 (<1%)
AEs leading to dose reduction or temporary discontinuation	1 (<1%)	4 (<1%)
AEs leading to dose reduction or temporary discontinuation related to study treatment	0	3 (<1%)

Sources: EUA request Table 41 and 42 and analysis of the EPIC-HR ADAE dataset.

Deaths

A total of 10 deaths occurred in EPIC-HR by the interim analysis, all in the placebo group and all related to COVID-19. The AEs resulting in death included COVID-19 pneumonia (n=5), COVID-19 (n=2), hypoxia (n=1), acute respiratory distress syndrome (n=1), and acute respiratory failure (n=1). The subjects who died were older than the general study population (median age 70 years, range 52 to 84) and generally had multiple comorbidities associated with severe COVID-19.

With the topline data from all enrolled subjects, an additional 3 placebo recipients died, for a total of 13 deaths in EPIC-HR (all among placebo recipients).

Serious Adverse Events

A total of 59 subjects reported SAEs in the interim analysis, 13 (2%) Paxlovid recipients versus 46 (7%) placebo recipients. Most SAEs were in the infections and infestations system organ class (SOC) [8 (1%) Paxlovid recipients versus 35 (5%) placebo recipients], with COVID-19 pneumonia being the most common single SAE [4 (<1%) Paxlovid recipients versus 21 (3%) placebo recipients]. No SAEs reported in more than one subject were reported more frequently in the Paxlovid versus placebo group.

(b) (4)

Similar overall SAE results were observed in the topline safety results from all enrolled subjects (18/1109, or 2%, Paxlovid recipients versus 74/1115, or 7%, placebo recipients reported SAEs); a breakdown of specific SAEs was not included in the topline results.

Adverse Events Leading to Discontinuation of Study Drug

A total of 45 subjects discontinued study treatment due to AEs in the interim analysis, 16 (2%) Paxlovid recipients versus 29 (4%) placebo recipients. AEs leading to discontinuation reported in more than 1 Paxlovid recipient included nausea (n=5 Paxlovid recipients and 2 placebo recipients), vomiting (n=4 Paxlovid recipients and 0 placebo recipients), and creatinine renal clearance decreased (n=2 Paxlovid recipients and 4 placebo recipients, also including glomerular filtration rate abnormal or decreased).

Similar numbers of overall AEs leading to discontinuation were observed in the topline safety results from all enrolled subjects (23/1109, or 2%, Paxlovid recipients versus 47/1115, or 4%, placebo recipients discontinued study drug due to AEs); a breakdown of specific AEs leading to discontinuation of study drug was not included in the topline results.

Common Adverse Events

A total of 133/672 (20%) Paxlovid recipients and 151/677 (22%) placebo recipients reported an AE by Day 34 in the interim analysis. The most common AEs are shown in Table 13. AEs reported in more Paxlovid versus placebo recipients with a difference of at least 3 subjects include dysgeusia (32 versus 1 subject), diarrhea (26 versus 13 subjects), vomiting (9 versus 2 subjects), hypertension (6 versus 1 subject), chills (5 versus 0 subjects), anosmia (3 versus 0 subjects), and oropharyngeal pain (3 versus 0 subjects), among Paxlovid and placebo recipients, respectively. AEs reported in more placebo versus Paxlovid recipients (difference of at least 3 subjects) include COVID-19 pneumonia (23 versus 5 subjects), COVID-19 (12 versus 3 subjects), fibrin D-dimer increased (11 versus 3 subjects), alanine aminotransferase increased (10 versus 4 subjects), pneumonia (7 versus 2 subjects), dyspnea (6 versus 3 subjects), hypoxia (5 versus 0 subjects), fatigue (5 versus 2 subjects), erythema (4 versus 0 subjects), acute respiratory failure (4 versus 1 subject), and pain (3 versus 0 subjects), among placebo and Paxlovid recipients, respectively.

Table 13: Adverse Events Reported by ≥1.0% of Subjects in Either Treatment Group in EPIC-HR through Day 34, Interim Analysis

Preferred Term	Paxlovid n=672	Placebo n=677
Subjects with at least 1 AE	133 (20%)	151 (22%)
Dysgeusia	32 (5%)	1 (<1%)
Diarrhea	26 (4%)	13 (2%)
Nausea	13 (2%)	14 (2%)
Headache	10 (1%)	11 (2%)
Vomiting	9 (1%)	2 (<1%)
Pyrexia	8 (1%)	7 (1%)
COVID-19 Pneumonia	5 (<1%)	23 (3%)

Alanine aminotransferase increased	4 (<1%)	10 (1%)
COVID-19	3 (<1%)	12 (2%)
Fibrin D-dimer Increased	3 (<1%)	11 (2%)
Pneumonia	2 (<1%)	7 (1%)

Sources: EUA request Table 43 and analysis of the EPIC-HR ADAE dataset.

Similar AE results were observed in the topline safety results from all enrolled subjects. A total of 251/1109, or 23%, Paxlovid recipients versus 266/1115, or 24%, placebo recipients reported AEs. A similar pattern of specific AEs was also seen, except that an imbalance in vomiting AEs was no longer observed with the additional data (among all enrolled subjects, 12/1109, or 1%, Paxlovid recipients versus 9/1115, or 1%, placebo recipients reported an AE of vomiting). Among all enrolled subjects, the AEs reported in $\geq 1\%$ of Paxlovid recipients (rounding up) that occurred at a greater frequency (≥ 5 subject difference) than in the placebo group were dysgeusia (62/1109 or 6% versus 3/1115 or <1%), diarrhea (34/1109 or 3% versus 18/1115 or 2%), hypertension (7/1109 or 1% versus 2/1115 or <1%), and myalgia (7/1109 or 1% versus 2/1115 or <1%, among Paxlovid versus placebo recipients, respectively).

Grade 3 and Above Adverse Events

A total of 21/672 (3%) Paxlovid recipients and 58/677 (9%) placebo recipients reported an adverse event with toxicity grade of 3 or greater. The only grade 3 or higher AEs reported in more than one Paxlovid recipient were creatinine renal clearance decreased (3 Paxlovid recipients versus 4 placebo recipients), COVID-19 pneumonia (3 Paxlovid recipients versus 19 placebo recipients), and blood fibrinogen decreased (2 Paxlovid recipients versus 0 placebo recipients). Similar overall results were observed in the topline safety results from all enrolled subjects.

Adverse Events Considered Related to Study Treatment

A total of 49/672 (7%) Paxlovid recipients and 29/677 (4%) placebo recipients reported an AE considered related to the study treatment in the interim analysis. The most common related AEs are shown in Table 14. Related AEs reported in more Paxlovid versus placebo recipients (difference of at least 2 subjects) include dysgeusia (25 versus 1 subject), diarrhea (13 versus 2 subjects), vomiting (5 versus 1 subject), dyspepsia (5 versus 2 subjects), and dizziness (2 versus 0 subjects among Paxlovid versus placebo recipients, respectively). No related AEs were reported in more placebo than Paxlovid recipients with a difference of at least 2 subjects. A total of 94% (104/111) of all AEs reported were graded as mild to moderate. None of the grade 3 or higher related AEs were reported in more than one subject. Adverse events considered related to study treatment were not reported in the topline results of all enrolled subjects.

Table 14: AEs Considered Related To Study Treatment* Reported in More than One Subject in Either Treatment Group in EPIC-HR through Day 34, Interim Analysis

Preferred Term	Paxlovid n=672	Placebo n=677
Subjects with at least 1 Related AE	49 (7%)	29 (4%)
Dysgeusia	25 (4%)	1 (<1%)
Diarrhea	13 (2%)	2 (<1%)
Nausea	6 (<1%)	7 (1%)
Vomiting	5 (<1%)	1 (<1%)
Dyspepsia	5 (<1%)	2 (<1%)
Gastroesophageal reflux disease	2 (<1%)	1 (<1%)
Dizziness	2 (<1%)	0
Abdominal pain upper	1 (<1%)	2 (<1%)
Rash	1 (<1%)	2 (<1%)

*Considered related to study treatment by the investigator

Sources: EUA request Table 44 and analysis of the EPIC-HR ADAE dataset.

Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs in EPIC-HR, based on the findings in the nonclinical studies, include hemodynamic events, inflammatory events, and thyroid-related events. Although the Applicant did not include an analysis of the AESIs in the EUA submission, a review of the submitted data related to the AESIs in the interim analysis showed the following:

- Hemodynamic Events

- Overall, there were no notable differences in the changes in vital sign parameters over time between the Paxlovid and placebo groups.
- As noted above, more Paxlovid recipients had an AE of hypertension (6 Paxlovid recipients versus 1 placebo recipient). Among the 6 Paxlovid recipients with an AE of HTN:
 - The median age was 60 years (range 40 to 71)
 - *The placebo recipient was 44-years-old*
 - The AE onset day was 2, 4, 4, 4, 5, and 25 (*9 for the placebo recipient*)
 - One AE was graded as moderate (onset Day 4) and one was graded as severe (onset day 5), but the remainder were graded as mild.
 - All but one of the Paxlovid recipients, as well as the placebo recipient, were given additional concomitant treatment for the AE of hypertension.
 - None of the hypertension AEs were categorized as SAEs or as related to treatment, and none resulted in discontinuation of study treatment.
 - *In the topline results of all enrolled subjects, a similar pattern for hypertension AEs was seen. Hypertension AEs were reported in 7 Paxlovid recipients (4 mild, 2 moderate, 1 severe) and 2 placebo recipients (one mild, one moderate). In addition, one grade 4 SAE of “hypertensive crisis” was reported in a Paxlovid recipient.*
- Numerically less Paxlovid versus placebo recipients had an AE of hypotension or orthostatic hypotension (1 Paxlovid recipient versus 3 placebo recipients).
- *Given the nonclinical findings (increased blood pressure in the safety pharmacology study in monkeys with a clinical margin of 1.9), the imbalance*

in hypertension AEs, and the temporal clustering of 5 of 6 events during the 5-day treatment period, this may be related to study treatment despite the lack of a general increase in blood pressure during treatment in the treated population. However, this AE was infrequent. Hypertension should be included as an adverse reaction with Paxlovid in Section 6 of the fact sheet.

- Inflammatory Events
 - Overall, there were no clinically significant differences in the changes in platelet levels, leukocytes, lymphocytes, neutrophils, C-reactive protein, fibrinogen, ferritin, procalcitonin, or d-dimer over time between the Paxlovid and placebo groups, and any possible trends favored the Paxlovid group (i.e., there was a slight trend towards a faster decrease in some inflammatory markers like d-dimer and fibrinogen in subjects receiving Paxlovid).
 - Given that the disease being treated (COVID-19) can lead to inflammation, separating out AEs of inflammatory events from the sequelae of COVID-19 is challenging. However, in general, there were no concerning trends regarding AEs related to inflammatory events suggesting a higher incidence among Paxlovid recipients.
 - *At this point, there are no clinical findings related to inflammatory events that warrant inclusion in the fact sheet.*
- Thyroid-related Events
 - Overall, there were no notable differences in the changes in free thyroxine (free T4) or thyrotropin (thyroid stimulating hormone) over time between the Paxlovid and placebo groups.
 - In regards to thyroid-related AEs:
 - A total of 2 Paxlovid recipients versus 1 placebo recipient had AEs of blood thyroid stimulating hormone increased. These started on Day 2 (Paxlovid recipient) and Day 14 (Paxlovid and placebo recipient). None were SAEs.
 - Among the 2 Paxlovid recipients, the events were mild and considered not related to study treatment.
 - In the placebo recipient, the event was graded as moderate and was considered related to study treatment.
 - A total of 1 Paxlovid recipient versus 0 placebo recipients had an AE of thyroxine increased. This AE was mild, nonserious, not considered related to study treatment, started on Day 6 and ended on Day 40.
 - *At this point, there are no clinical findings for thyroid-related events that warrant inclusion in the fact sheet.*

Laboratory Findings, Vital Signs, and ECG Results

Changes in laboratory parameters and vital signs from baseline were similar between the Paxlovid and placebo groups in the interim analysis (these data were not provided in the topline results of all enrolled subjects that were provided during the EUA review). ECG results from the sentinel group in EPIC-HR were previously reviewed (see IND 153517 SDN 62 review from 8/27/2021 in DARRTS); unblinded ECG data did not show any notable changes in ECG intervals or appreciable

differences in ECG parameters on Days 3, 5, and 14 between 34 Paxlovid recipients versus 33 placebo recipients.

Please see the discussion of the imbalance in AEs of hypertension in the section above.

Safety Issues of Concern based on Ritonavir Labeling

The FDA-approved label for ritonavir, which is for a higher 600 mg bid ritonavir dose given indefinitely for use as part of HIV treatment, includes the following contraindications and warnings and precautions (in addition to those related to drug-drug interactions, which will be addressed separately) that could be relevant to the population proposed for use under the EUA; it is unclear how many of these safety issues would be a concern with the lower 100 mg bid dose and five-day course proposed for Paxlovid. AEs or other findings related to these safety issues from the interim analysis in EPIC-HR are described below.

- **Allergic/hypersensitivity reactions (including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome)**
 - There were no cases of serious allergic or hypersensitivity reactions, and AEs in the skin and subcutaneous disorders SOC were well-balanced between treatment groups.
 - Overall, 5 Paxlovid recipients versus 7 placebo recipients had AEs in the skin and subcutaneous disorders SOC.
 - A total of 3 Paxlovid recipients and 2 placebo recipients had AEs of rash or rash maculo-papular (one graded as severe in each treatment group, the rest graded as mild).
 - One placebo recipient had mild urticaria.
 - One Paxlovid recipient had mild pruritus.
- **Hepatotoxicity**
 - Hepatotoxicity Adverse Events
 - A total of 20 subjects had AEs related to hepatotoxicity: 7 Paxlovid recipients versus 13 placebo recipients
 - 14 subjects (4 Paxlovid recipients and 10 placebo recipients) had alanine aminotransferase increased
 - 5 subjects (2 Paxlovid recipients and 3 placebo recipients) had aspartate aminotransferase increased
 - 3 subjects (1 Paxlovid recipient and 2 placebo recipients) had hepatic enzyme increased
 - One subject each had liver injury (placebo recipient), hepatitis toxic (Paxlovid recipient), and hyperbilirubinemia (Paxlovid recipient)
 - The only two subjects with hepatotoxicity AEs considered related to study treatment were placebo recipients
 - The only hepatotoxicity SAE was in a placebo recipient
 - A total of 1 Paxlovid recipient and 4 placebo recipients had grade 3 or higher hepatotoxicity AEs
 - Subjects Meeting the Sponsor's Hepatotoxicity Criteria

- A total of 7 Paxlovid recipients and 11 placebo recipients met hepatotoxicity criteria.
 - Among Paxlovid recipients: 4 subjects had hepatic transaminase elevations exceeding 5X the ULN and 1 subject each had hepatitis toxic, cholestasis, and hyperbilirubinemia.
 - None of the Paxlovid recipients met Hy's Law Criteria
 - Among placebo recipients, 10 subjects had hepatic transaminase elevations exceeding 5X the ULN and 1 subject had liver injury
 - Laboratory Changes: There were no notable differences in the changes in prothrombin time, bilirubin, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase over time between the Paxlovid and placebo groups.
- **Pancreatitis**
 - No subjects reported AEs of pancreatitis or elevated amylase or lipase.
 - Of note, amylase and lipase were not routinely collected as part of the laboratory assessments.
- **PR interval prolongation (with second and third degree heart block)**
 - No subjects had AEs of heart block or PR interval prolongation.
 - A total of five subjects had any AEs related to heart rate or rhythm: four subjects (2 placebo recipients and 2 Paxlovid recipients) had palpitations, one considered serious and related and leading to discontinuation of study treatment (Paxlovid recipient, discussed under the SAE section), and one placebo recipient had sinus tachycardia.
 - As noted in the ECG section above, there were no notable changes in ECG intervals with treatment observed among the subjects in the sentinel cohort in EPIC-HR.
- **Total cholesterol and triglycerides elevations**
 - One subject (placebo recipient) had an AE of mild hypertriglyceridemia. No AEs were reported related to total cholesterol levels.
 - Of note, total cholesterol and triglycerides were not routinely collected as part of the laboratory assessments.
- **New onset or exacerbations of diabetes mellitus or hyperglycemia**
 - A total of 17 subjects had AEs related to exacerbations of diabetes mellitus or hyperglycemia (preferred terms: blood glucose increased, hyperglycemia, impaired fasting glucose, diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus inadequate control, and glycosylated hemoglobin increased): 7 Paxlovid recipients and 10 placebo recipients
 - None of the AEs were serious
 - The only AE that was considered related or led to study drug withdrawal was in a placebo recipient
 - The AEs were graded higher than moderate in 2 Paxlovid recipients and 4 placebo recipients
 - There was no temporal pattern
 - There were no notable differences in the changes in glucose over time between the Paxlovid and placebo groups.
- **Redistribution/accumulation of body fat**

- No AEs were reported relating to redistribution/accumulation of body fat.
- Weight was only recorded at screening
- **Spontaneous bleeding in patients with hemophilia**
 - The only AE reported that had to do with bleeding, vaginal hemorrhage, was reported in both a Paxlovid recipient and a placebo recipient.
 - No subjects had hemophilia

Assessment: From data available with the EPIC-HR interim analysis, there was no apparent signal observed for the above safety issues of concern in ritonavir labeling when comparing subjects who received 5 days of Paxlovid (containing 100 mg bid ritonavir) versus placebo. The lack of these safety findings may be due to the low dose and short course of ritonavir used with Paxlovid for the proposed authorized use; however, the small numbers in the trial preclude any formal conclusions. Of the above listed safety issues of concern, the Sponsor has proposed to include hepatotoxicity in the warnings and precautions of the Paxlovid fact sheet (in addition, history of clinically significant hypersensitivity reactions to the active ingredients is included in the contraindications section). This is consistent with labeling for the FDA-approved product VIEKIRA PAK, which included ritonavir 100 mg daily and was administered for 12-24 weeks. Based on the safety findings from EPIC-HR and the short course and low dose of ritonavir, inclusion of hepatotoxicity in the warnings and precautions of Paxlovid, without the other ritonavir labeled warnings and precautions listed above, is reasonable.

Special Populations:

A total of 112 subjects in the EPIC-HR interim analysis safety database (55 Paxlovid recipients and 57 placebo recipients) were flagged as having received or expected to receive COVID-19 monoclonal antibody treatment. Among these subjects:

- AEs were reported in 13/55 (24%) Paxlovid recipients and 18/57 (32%) placebo recipients.
- Treatment-related AEs were reported in 6/55 (11%) Paxlovid recipients (dysgeusia [n=4], diarrhea [n=1], and dry mouth [n=1], all grade 1) and 1/57 (2%) placebo recipients
- SAEs were reported in 1/55 (2%) Paxlovid recipients and 4/57 (7%) placebo recipients (none fatal)
- Grade 3 or higher AEs were reported in 1/55 (2%) Paxlovid recipients (worsening of COVID-19) and 8/57 (14%) placebo recipients

These proportions between Paxlovid versus placebo recipients are similar to the overall population and do not raise safety concerns about the concomitant use of Paxlovid with COVID-19 monoclonal antibody treatment.

A separation of safety data by having received or expected to receive COVID-19 monoclonal antibody treatment was not included with the topline submission of data from all enrolled subjects.

Supplementary Safety Data (Phase 1 Trials)

Key safety data from the supplementary trials submitted with this EUA include the following:

- **Study C4671001 (the first-in-human single ascending dose, multiple ascending dose study)**
 - Single ascending dose up to 1500 mg NIR and 750 mg NIR co-administered with 100 mg ritonavir (n=4 per dose):
 - There were no serious or severe AEs and no dose-related trends in number of AEs.
 - No single AE was reported in more than one subject.
 - The only discontinuation due to an AE was due to COVID-19.
 - Multiple ascending dose up to 500 mg NIR coadministered with 100 mg ritonavir bid x 10 days (19 NIR/r recipients across dose levels, with 4 subjects receiving 75 mg NIR, 8 subjects receiving 250 mg NIR, and 7 subjects receiving 500 mg NIR bid, and 10 placebo recipients):
 - There were no serious or severe AEs, discontinuations due to an AE, or dose-related trends in AEs.
 - AEs reported in more than one subject (across dose levels) included:
 - Diarrhea (n=4 NIR/r recipients across dose levels, and n=1 placebo recipients)
 - Blood thyroid stimulating hormone increased (n=3 NIR/r recipients and n=2 placebo recipients)
 - Dysgeusia (n=3 NIR/r recipients)
 - Fatigue (n=2 NIR/r recipients, n=1 placebo recipient)
 - Headache (n=2 NIR/r recipients)
 - Single suprathreshold dose (2250 mg NIR with 100 mg ritonavir, n=10) versus placebo with 100 mg ritonavir (n=10)
 - All AEs were mild and frequency was the same between the placebo and the treatment group (30% each group reported AEs), and no AE was reported by more than one NIR/r recipient.
 - ECG results:
 - See IND 153517 SDN 60 review from 8/27/2021 in DARRTS; there was no evidence of clinically relevant QTc interval prolongation with the suprathreshold dose versus placebo.
 - Currently, data needed to support inclusion of ECG and QT information in the EUA Fact Sheet have not been submitted and reviewed; therefore, such data will not be included in the EUA Fact Sheet (see also Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviews from 10/14/2021 and 11/18/2021 in DARRTS).
- **Study C4671010 (hepatic impairment study: preliminary topline report)**
 - There were no SAEs, and the only AE reported in more than one subject was dysgeusia (n=2).
- **Study C4671011 (renal impairment study)**
 - This study enrolled subjects with normal renal function (n=10) and mild, moderate, or severe renal impairment (n=8 per group) as per the table

below (taken from the C4671011 clinical study report) who received 100 mg NIR on Day 1 and 100 mg ritonavir on Day 1 and at -12 hours, +12 hours, and +24 hours in relation to the Day 1 dose.

Table 2. Renal Function Categories by eGFR Ranges

Cohort	Renal impairment ^a	Estimated eGFR ^b (mL/min)
1	Moderate renal impairment	≥30 to <60
2	Mild renal impairment	60 – <90
3	None (normal)	≥90
4	Severe renal impairment	<30 and not requiring dialysis

a. Stages of renal impairment are based on KDOQI Clinical Practice Guidelines for CKD.³

b. Estimate of eGFR based on CKD-EPI formula. The average of the 2 screening eGFR values were used for group assignment.

Source: [Appendix 16.1.1](#)

- A higher proportion of subjects with severe renal impairment reported AEs (5/8 (62.5%) versus 1/8, 1/8, and 2/10 for the moderate renal impairment, mild renal impairment, and normal renal function groups, respectively). A total of 17 of the 22 all-causality AEs in the study were among subjects with severe renal impairment. AEs reported by >1 subject included:
 - Headache (1 subject with moderate renal impairment and 2 subjects with normal renal function)
 - Dysgeusia (2 subjects with severe renal impairment)
 - Asthenia (2 subjects with severe renal impairment)
 - Dry mouth (2 subjects with severe renal impairment)
- A higher proportion of subjects with severe renal impairment reported treatment-related adverse events (2/8, 25%, versus 0/8, 0/8, and 0/10 for the moderate renal impairment, mild renal impairment, and normal renal function groups respectively). Treatment-related adverse events included mild dysgeusia (n=2) and mild dry mouth (n=2, same two subjects as for dysgeusia).
- One subject (with severe renal impairment) reported 3 SAEs (severe pulmonary edema, moderate acute kidney injury, and moderate pneumonia) and discontinued the study due to these AEs. This one subject was responsible for 11 of the 22 AEs in the study (in addition to the three SAEs, mild asthenia, mild anemia, moderate bradycardia, moderate hyperkalemia, mild hyponatremia, moderate hypotension, moderate metabolic acidosis, and mild thrombocytopenia).
 - This subject was a 75-year-old white female with diabetes mellitus type 2, chronic kidney disease stage 4 (baseline creatinine 2.21 mg/dL), hypertension, anemia, depression, metabolic acidosis, history of left nephrectomy, history of renal cell carcinoma, and history of aortic valve replacement who received NIR 100 mg on Day 1 and 100 mg ritonavir at -12 hours, with NIR, at +12 hours, and at +24 hours. On Day 2, her creatinine had increased to 3.45 mg/dL and her potassium increased to 6.3 mmol/L, and she was sent to the emergency room where she was diagnosed with likely pneumonia based on a chest X-ray with an airspace opacity. She subsequently developed pulmonary edema and fluid overload necessitating ICU admission on Day 3. She subsequently

recovered and was discharged from the hospital on Day 7. The investigator thought her SAEs and AEs were unrelated to study drug.

- AEs experienced by the other 4/8 subjects with severe renal impairment who reported AEs included dry mouth (n=2), nausea (n=1), asthenia (one additional subject), and dysgeusia (n=2).
- There were no deaths in the study.

Reviewer Comment: Two safety issues are raised by the supplementary safety data from the Phase 1 trials:

1. *Data needed to support EUA Fact Sheet information pertaining to the QT interval/cardiac electrophysiology describing suprathreshold NIR/r dosing ECG findings have not been submitted for IRT review.*
2. *No concerning safety findings were seen in the 7 subjects who received 500 mg NIR with 100 mg ritonavir bid x 10 days in Study C4671001. However, there was an imbalance in safety findings between subjects with severe renal impairment and subjects with normal to moderate renal impairment in Study C4671011 who all received 100 mg NIR as a single dose administered with ritonavir, with one of the eight subjects with severe renal impairment developing an SAE of moderate acute kidney injury the day after receiving NIR. While it is unclear if these safety findings were related to NIR receipt or to the increased comorbidities generally associated with severe renal impairment, this finding raises safety concerns about NIR/r dosing in patients with severe renal impairment (as the therapeutic dose would be higher than 100 mg NIR administered with ritonavir); therefore, the fact sheet should convey that Paxlovid is not recommended in patients with severe renal impairment. An EUA condition of authorization should be for the sponsor to conduct a study of NIR/r for treatment of mild-to-moderate COVID-19 in patients with severe renal impairment, including patients on dialysis, to assess the safety and appropriate dose in this population.*

Noteworthy Drug Interactions

Paxlovid has multiple noteworthy drug interactions. Individuals taking concomitant medications that could have clinically significant drug interactions with Paxlovid were excluded from EPIC-HR. Please see *Section XI. Human Clinical Pharmacology* for more information on noteworthy drug interactions.

X. Specific Populations

Dosing Considerations for Specific Populations

Pediatrics

As of December 2, 2021 over 7 million children have tested positive for COVID-19 in the United States, Puerto Rico, and Guam (<https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/> accessed December 10, 2021). Based on these data, for the week ending

December 2, 2021, children represented 22.4% of the weekly reported cases. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), there is prospect of benefit for this population.

Safety and PK data are not available in pediatrics. The inclusion of pediatric patients 12 years and older and weighing at least 40 kg in the authorized use is supported by the following: 1) the extrapolation of efficacy is deemed appropriate as the course of the disease and the response to treatment are sufficiently similar in adults and children; 2) the systemic NIR/r exposures are expected to be comparable in adolescents and adult patients administered the adult dose (see details in Pharmacometrics Review); and 3) the dose of NIR/r 300/100 mg BID was well-tolerated in adults weighing 42-158 kg in the Phase 2/3 EPIC-HR Study.

Population PK simulations were conducted for pediatric patients ≥ 12 to < 18 years of age using the CDC National Center for Health Statistics growth chart. These simulations suggest that a dose of NIR/r 300 mg/100 mg BID in adolescents provide higher geometric mean NIR AUC₀₋₁₂, C_{max} and C_{trough} by 32%, 37% and 25%, respectively, as compared to adults receiving the same dose. In comparison, a dose of NIR/r 150 mg/100 mg BID in adolescents provided lower geometric mean NIR AUC₀₋₁₂, C_{max} and C_{trough}, by 14%, 6% and 22%, respectively, as compared to adults. The NIR/r 300 mg/100 mg BID dose is expected to maintain efficacious trough concentrations above the EC90 over the entire dosing interval and are not expected to pose additional safety risks since a suprathreshold dose of 2250 mg NIR (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 was well tolerated in ten healthy adult subjects (See *Section XI. Human Clinical Safety*). The geometric mean C_{max} and AUC_{inf} at this suprathreshold dose was 15.940 $\mu\text{g/mL}$ and 188.800 $\mu\text{g}\cdot\text{hr/mL}$, respectively, which are 4 fold of those predicted in adolescents at the recommended NIR/r dose.

Additional simulations were conducted to determine the predicted C_{max} for pediatrics 12 years and older by weight band using NHANES data (See Figure 4, Pharmacometrics Review). In these simulations, the 95th percentile of predicted C_{max} in adults was used as the safety threshold. While the adult dose was deemed acceptable in adolescent patients ≥ 40 kg, approximately 50% of the pediatric patients < 40 kg were predicted to achieve C_{max} values above this safety margin (See *Appendix: Pharmacometrics Review*). For this reason, the adult dose is only recommended for pediatric patients weighing ≥ 40 kg.

Based on the totality of evidence to support the prospect of benefit, and the fact that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of Paxlovid for the treatment of mild-to-moderate COVID-19 should also include adolescents who are 12 years of age and

older and who weigh at least 40 kg. No dose adjustment is recommended in pediatric individuals who weigh at least 40 kg and are 12 years of age and older. Paxlovid is not recommended for pediatric individuals weighing less than 40 kg or those less than 12 years of age. A pediatric clinical trial which will enroll children across a broad age range is planned.

Renal Impairment

The primary route of elimination of NIR when administered with ritonavir is renal excretion of intact drug. In a dedicated renal impairment study (Study 1011) subjects received a single dose of 100 mg NIR and ritonavir 100 mg administered at -12, 0, 12, and 24 hours relative to NIR dosing (0.33 times the recommended dose). This NIR dose was chosen due to the less than dose proportional increase in exposures within the 250 mg to 750 mg dose range evaluated and anticipated increased 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. Mean AUC_{inf} values of NIR in patients with mild (eGFR 60 to <90 mL/min), moderate (eGFR \geq 30 to <60 mL/min), and severe renal impairment (eGFR <30 mL/min) were 24%, 87% and 204% higher than that of healthy volunteers, respectively (Table 15).

Table 15. Study 1011: Plasma and Urine Nirmatrelvir PK Parameters

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
N1,n	10,10	8,8	8,6	8,7
AUC_{inf} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
C_{max} ($\mu\text{g}/\text{mL}$)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
C_{12} ($\mu\text{g}/\text{mL}$)	0.34 (35)	0.44 (30)	0.79 (33)	1.21 (33)
$T_{1/2}$ (hr)	7.73 \pm 1.82	6.60 \pm 1.53	9.95 \pm 3.42	13.37 \pm 3.32
T_{max} (hr)	2 (1- 4)	2 (1- 3)	2.5 (1- 6)	3 (1- 6)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)

Source: Study 1011

Geometric mean (%CV) for all: except Median (Range) for T_{max} and arithmetic mean \pm SD for $t_{1/2}$

N1 = Number of subjects contributing to the summary statistics.

n = Number of subjects contributing to the summary statistics for $t_{1/2}$, AUC_{inf} , CL/F and VZ/F

Ae = amount excreted

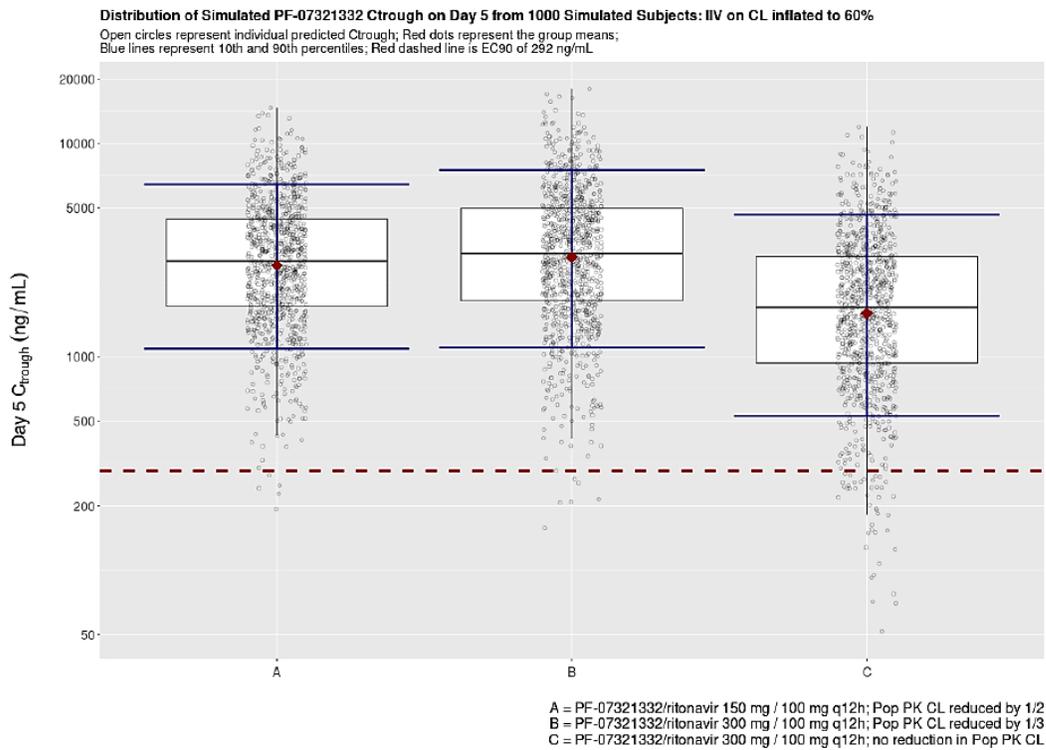
A preliminary population PK model was used to simulate C_{trough} concentrations in the following scenarios of reduced NIR clearance (Figure 3):

1. Clearance reduced by one-third to account for the 24% increase in AUC_{inf} in mild renal impairment, and dosed with 300/100 mg NIR/r twice daily
2. Clearance reduced by one-half to account for the 87% increase in AUC_{inf} in moderate renal impairment, and dosed with 150/100 mg NIR/r twice daily
3. No reduction in CL and dosed with 300/100 mg NIR/r twice daily (reference group)

Median C_{trough} values in all three scenarios exceeded the EC_{90} (292 ng/ml) shown to be efficacious in EPIC-HR. In a proof-of-concept evaluation, simulated NIR

exposures in subjects with moderate renal impairment with the proposed NIR/r dose reduction were comparable to those in subjects with normal renal function (See Figure 5, *Appendix 1: Pharmacometrics Review*). NIR/r was generally safe and well tolerated in subjects with mild and moderate renal impairment in Study 1011.

Figure 3. Predicted Nirmatrelvir C_{trough} by Dosing Regimen



Based on these simulations, no dose adjustment is recommended in patients with mild renal impairment. In patients with moderate renal impairment, the dose of Paxlovid should be reduced to 150 mg NIR and 100 mg ritonavir twice daily for 5 days. To mitigate the potential that this modified dose will lead to medication errors with the blister card packaging, specific counseling should be specified in the fact sheets and specific instructions with dispensing information should be provided to pharmacists.

Study 1011 noted a higher incidence of adverse events in patients with severe renal impairment (see *Section IX. Human Clinical Safety*). Given the 204% increase in AUC_{inf} and anticipated higher exposures at the clinical NIR dose of 300 mg BID, Paxlovid is not recommended in patients with severe renal impairment until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

Hepatic Impairment

Hepatic elimination is not expected to be a major route of elimination for NIR based on Phase 1 data. In plasma, the only drug-related entity was unchanged NIR. Preliminary unaudited PK data from an ongoing hepatic impairment study (Study 1010) of subjects with moderate hepatic impairment receiving a single dose of NIR 100 mg and 4 doses of ritonavir 100 mg at -12 hr, 0 hr, 12 hr, and 24 hr showed no meaningful impact of hepatic impairment on the PK of NIR compared to administration of NIR with ritonavir in healthy subjects with normal hepatic function (Table 16). These data reflect the full cohort of subjects planned for enrollment in this study.

Table 16. Study 1010: Unaudited Nirmatrelvir Plasma PK Parameters

	Normal Hepatic Function	Moderate Hepatic Impairment (Child-Pugh Class B)
N	8	8
AUC _{inf} (µg.hr/mL)	15.24 (36)	15.06 (43)
C _{max} (µg /mL)	1.89 (20)	1.92 (48)
T _{1/2} (hr)	7.21 ± 2.10	5.45 ± 1.57
T _{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)

Source: Study 1010

Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for t_{1/2}
 N = Number of subjects contributing to the summary statistics

No dose adjustment is needed 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 NIR or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, Paxlovid is not recommended for use in patients with severe hepatic impairment.

Pregnancy and Lactation

The need for dose adjustment in pregnant or lactating women has not been established due to the lack of PK and safety data in these patient populations.

Nonclinical Safety Considerations for Pregnancy and Lactation

- In an embryo-fetal development study with NIR, reduced fetal body weights following oral administration of NIR to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of Paxlovid. No other adverse developmental outcomes were observed in animal reproduction studies with NIR at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of Paxlovid.
- In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of Paxlovid.

- In an ongoing pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered NIR at maternal systemic exposure (AUC₂₄) approximately 8 times higher than clinical exposures at the authorized human dose of Paxlovid. No body weight changes in the offspring were noted at maternal systemic exposure (AUC₂₄) approximately 5 times higher than clinical exposures at the authorized human dose of Paxlovid.
- Please see *Section XII* for detailed information.

XI. Human Clinical Pharmacology

Absorption, Distribution, Metabolism, and Excretion

The PK properties of NIR and ritonavir in healthy subjects are highlighted in Table 17.

Table 17. Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T _{max} (h), median	3.00 ^a	3.98 ^a
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14 ^c
V _z /F (L), mean	104.7 ^b	112.4 ^b
Elimination		
Major route of elimination	Renal elimination ^d	Hepatic metabolism
Half-life (t _{1/2}) (hr), mean	6.05 ^a	6.15 ^a
Oral clearance (CL/F), mean	8.99 ^b	13.92 ^b
Metabolism		
Metabolic pathways	Minimal ^d	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6% ^e	86.4% ^f
% drug-related material in urine	35.3% ^e	11.3% ^f

- 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.
- 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
- Red blood cell to plasma ratio.
- Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.

- e. Determined by ¹⁹F-NMR analysis following a single dose of NIR 300 mg oral suspension with 100 mg ritonavir administered at -12 hours, 0 hours, 12 hours, and 24 hours relative to NIR dosing.
- f. Determined by ¹⁴C analysis following 600 mg ¹⁴C-ritonavir oral solution.

Pharmacokinetics

The bioanalytical assays used to measure the concentrations of NIR and/or its metabolites in plasma and urine were adequately validated and found to be acceptable.

Healthy Subjects

Single and multiple dose PK of NIR were evaluated in healthy subjects and patients with COVID-19. Pharmacokinetic data in COVID-19 patients were not available prior to EUA action but will be provided when the EPIC-HR Study data for all randomized patients become available.

In healthy subjects, NIR exposures increased in a less than dose proportional manner following administration of an oral suspension formulation at single ascending NIR doses 250 mg to 750 mg, administered with 100 mg ritonavir or multiple ascending NIR/r doses of 75/100 mg BID to 500/100 mg BID for 10 days.

Ritonavir is administered with NIR as a CYP3A inhibitor resulting in higher systemic concentrations of NIR following single dose administration of the oral suspension formulation (Table 18). Pharmacokinetic parameters of NIR following single dose administration of the clinical 150mg tablet formulation (at a single dose of 300 mg NIR/100 mg ritonavir) are shown in Table 19.

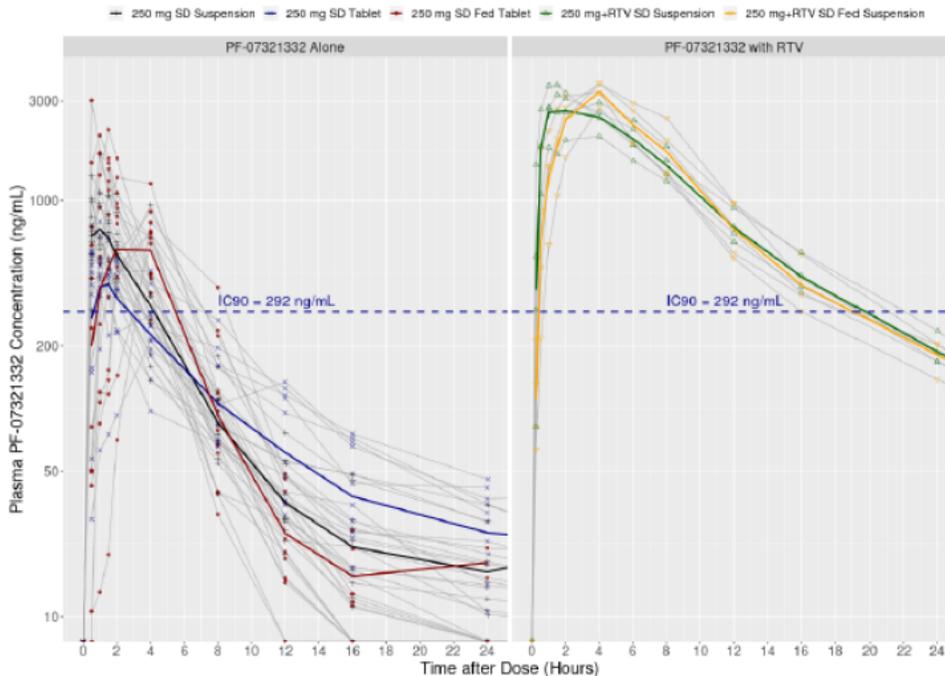
Table 18. Single Dose Pharmacokinetics of Nirmatrelvir Alone vs. Nirmatrelvir with Ritonavir in Healthy Subjects

	Geometric Mean (% CV)	
	AUC _{last} (µg.hr/mL)	C _{max} (µg /mL)
Nirmatrelvir alone ^a	3.32	0.88
Nirmatrelvir with Ritonavir ^b	27.6	2.88

a. 250 mg (oral suspension formulation)

b. 250 mg (oral suspension formulation with 100 mg ritonavir (tablet formulation) administered together

Figure 4. Observed NIR Plasma Concentration versus Time After Dose for NIR Dose of 250 mg in Study C4671001 Stratified by with and without Co-administration of Ritonavir



Repository artifact ID FI-21466304.

IC₉₀ = inhibitory concentration 90%; RTV = ritonavir; SD = single dose.

Symbols represent individual observations; Light grey lines represent individual profiles; Thick colored lines represent group median profiles; Dashed horizontal blue line represents the target exposure IC₉₀.

Excluded observations with time after dose >24 hours.

Table 19. Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects

PK Parameter (units)	Nirmatrelvir (N=12)	Ritonavir (N=12)
C _{max} (µg/mL)	2.21 (33)	0.36 (46)
AUC _{inf} (µg*hr/mL)	23.01 (23)	3.60 (47)
T _{max} (hr)	3.00 (1.02-6.00)	3.98 (1.48-4.20)
T _{1/2} (hr)	6.05 ± 1.79	6.15 ± 2.24

Represents data from 2 x 150 mg tablets of nirmatrelvir co-administered with ritonavir. Values are presented as geometric mean (% CV) except median (range) for T_{max} and arithmetic mean ± SD for T_{1/2}.

NIR pharmacokinetic parameters following a suprathereapeutic dose of 2250 mg (divided into 3 doses of 750 mg each administered at 0, 2 and 4 h) administered with ritonavir are presented in *Table 20*. The safety data, including AEs, laboratory abnormalities, vital signs, and ECGs indicate that NIR has an acceptable safety and tolerability profile in healthy adult subjects at suprathereapeutic exposures (See *Section XI. Human Clinical Safety*).

Table 20. Study 1001 Part 5: Descriptive summary of plasma NIR PK parameters

Parameter	NIR 250mg (suspension)/ritonavir 100mg
N	10

AUC _{inf} (µg.hr/mL)	188.80 (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

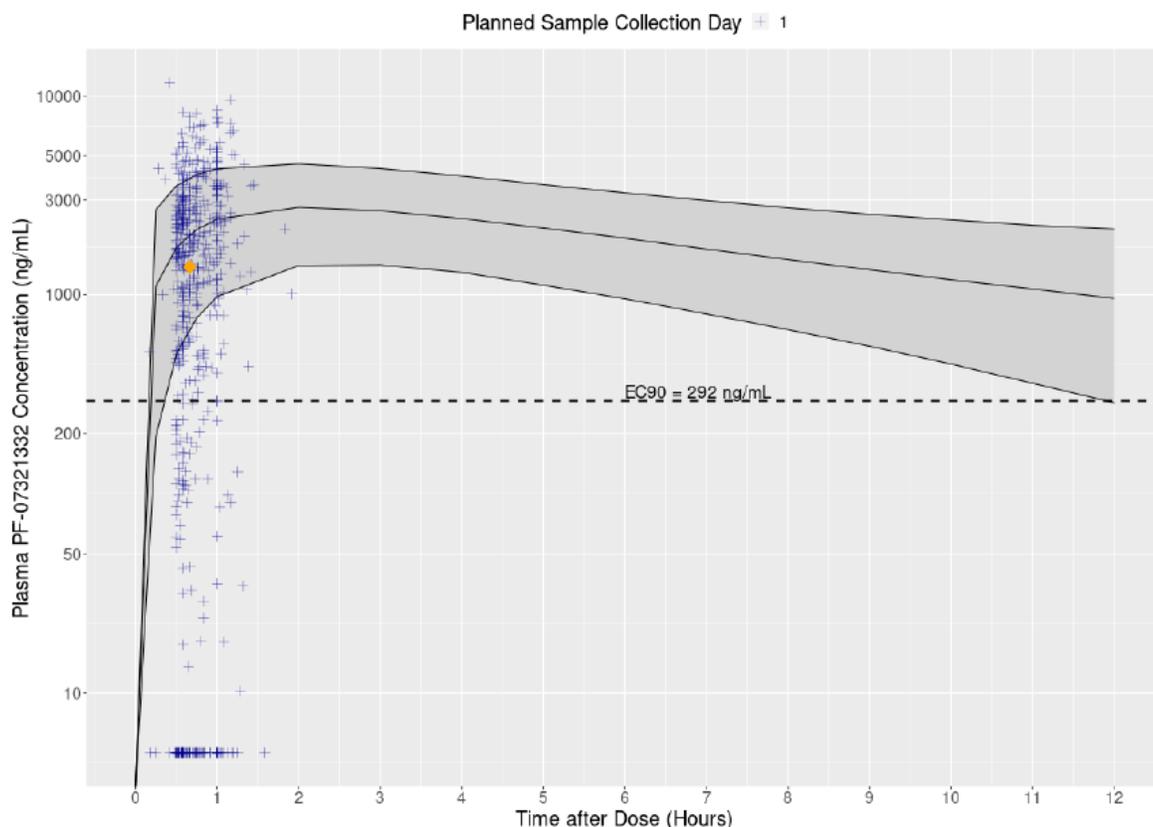
N = Total number of subjects in the treatment group

Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for t_{1/2}

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose. This recommendation follows what was done in the Phase 2/3 study 1005 and is also confirmed by population PK analysis.

Figure 5 shows the median and 90% prediction interval (PI) of plasma NIR concentration versus time after the first dose. The observed patient data collected in Study 1005 were overlaid on the simulated data. As shown in Figure 5, simulated NIR concentrations remain above the EC₉₀ for 12 hours after the first dose.

Figure 5. Mean and 90% prediction intervals for NIR concentrations based on 1000 simulations (NIR/3 300mg/100mg q12h after 1st dose) overlaid with observed data from Study 1005



Patients with COVID-19

In the Phase 2/3 EPIC-HR Study, one blood sample was scheduled to be collected on Day 1 (0.5 to 1.5 hr post dose) and on Day 5 (up to 2 hours pre-dose; otherwise, collected anytime post dose) for all subjects when feasible to remain at the study site. Optional PK samples were collected on either Day 2, 3, or 4 via home health visit, in-clinic visits, or self-collected whole blood microsample.

Sparse PK samples were submitted for review in the EUA and included approximately 45% of subjects (planned interim analysis). A total of 1,298 plasma NIR concentrations, including 1,068 evaluable samples and 230 (17.7%) BLQ samples, from 601 subjects with COVID-19 receiving NIR/r 300 mg/100 mg q12h for 5 days from EPIC-HR were available for analysis. There were 46 subjects who did not have any evaluable samples (all observations were BLQs).

Relevant sections of the EUA Fact Sheet will be updated when data from the Phase 2/3 EPIC-HR Study from all randomized patients are provided. Exposure-response analyses are not available.

Cardiac Electrophysiology

The effect of NIR on the QT interval has not been characterized. Ritonavir at a dose of 400 mg twice daily had no clinically relevant effect on QT interval.

Formulation Development of Nirmatrelvir

An extemporaneously prepared oral suspension and an uncoated 250 mg IR tablet were used in the first in human Study 1001. A 100 mg IR film-coated tablet was developed and was used in Phase 1 Study 1011 and in the sentinel cohort of 68 subjects in Phase 2/3 EPIC-HR Study.

The relative bioavailability of the 250 mg tablet versus 250 mg dose of the oral suspension was evaluated in Study 1001 in 12 healthy subjects. NIR plasma exposure for the tablet treatment was lower compared to the suspension. The test/reference ratios of the adjusted geometric means (90% CI) for NIR AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%), respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference).

A 150 mg IR film-coated tablet was subsequently developed and used in the pivotal Phase 2/3 EPIC-HR Study and other Phase 2/3 studies (Studies 1002 and 1006) as well as in Phase 1 Study 1014. The 150 mg tablet is the final formulation.

There are insufficient data to make a meaningful comparison between the 100 mg and 150 mg NIR tablets. A comparison of the concentrations between patients who received the 100 mg tablet used in the sentinel cohort of the Phase 2/3 study and the remaining patients who received the 150 mg tablet could not be accurately conducted given the sparse PK data submitted for EUA review.

Food Effect

Food effect was evaluated using an oral suspension formulation administered with ritonavir and a 250 mg tablet without ritonavir. In subjects administered the oral suspension with ritonavir, food did not significantly impact the exposure of NIR with an approximately 1.5% increase in AUC and 15% increase in C_{max} of NIR in the fed state as compared to fasted. In subjects administered the 250 mg tablet without ritonavir, AUC and C_{max} were approximately 1.5 and 2.4-fold higher compared to the fasted treatment, respectively.

Since NIR is intended for administration with ritonavir, food effect data using the oral suspension was used to inform dosing recommendations in Phase 2/3 studies. Paxlovid is recommended to be given without regard to food similar to how the clinical 150 mg tablet formulation was administered to patients with COVID-19 in the pivotal Phase 2/3 study. A dedicated food effect study using the final 150 mg NIR tablet formulation is planned.

Drug-Drug Interactions

Effect of NIR/r on Other Drugs

Potential drug-drug interaction liability of NIR as a perpetrator (effect of NIR on the absorption and disposition of other drugs) is based on *in vitro* studies of NIR alone.

The inhibitory potency of NIR was determined by measuring the activity of each 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.

NIR reversibly and time-dependently inhibited CYP3A4 and did not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 in vitro at clinically relevant concentrations (Table 21).

Table 21. Assessment of Risk for CYP Inhibition In Vitro Between NIR and Co-administered Substrates

Model	CYP	IC ₅₀ (μM)	R Value
Basic (R1) Reversible	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	CYP2A4/5 Midazolam	58.3	83.2
	CYP3A4/5 Testosterone	106	46.3
	CYP3A4/5 Nifedipine	45.1	107
Basic (R2) TDI		K_{i,u} (μM)	
	CYP2A4/5 Midazolam	15.5	26.4
	CYP3A4/5 Testosterone	13.9	30.8

The *in vitro* induction effect of NIR on CYP3A4, CYP2B6, CYP1A2, CYP2C9 and CYP2C19 was evaluated in cultured human hepatocytes at NIR concentrations of 0.01 to 200 μM . NIR 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 NIR on CYP3A was inhibition with no inhibition noted for the other enzymes (Table 22).

Table 22. Mechanistic Model of CYP Mediated DDI Risk Assessment of NIR

	Reversible Inhibition		TDI		Induction		AUC _{R1}	AUC _{R2}	AUC _{R3}	AUC _{R1,2}	AUC _{R1,2,3}
	Intestinal	Hepatic	Intestinal	Hepatic	Intestinal	Hepatic					
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

Ag = $1 / (1 + [I]g/Ki)$; Ah = $1 / (1 + [I]h/Ki)$; Bg = $kdeg,g / (kdeg,g + [I]g \cdot kinact / ([I]g + Ki))$; Bh = $kdeg,h / (kdeg,h + [I]h \cdot kinact / ([I]h + Ki))$; Cg = $1 + d \cdot Emax \cdot [I]g / ([I]g + EC50)$; Ch = $1 + d \cdot Emax \cdot [I]h / ([I]h + EC50)$; AUC_R = $1 / (Ag \cdot Bg \cdot Cg \cdot (1 - fg) + fg) \cdot 1 / (Ah \cdot Bh \cdot Ch \cdot fm + (1 - fm))$ ind = induction; rev = reversible; TDI or tdi = time-dependent inhibition.

In vitro transporter inhibition studies demonstrated that NIR inhibits P-gp ($[I]/IC_{50}=34$) and OATP1B1 ($R_1=1.11$). A clinical drug interaction study to assess the effect of NIR/r on dabigatran as a P-gp substrate (Study 1012) is currently ongoing. In vitro inhibition was not observed for BCRP, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Ritonavir is a potent inhibitor of CYP3A4 and P-gp.

A clinical drug interaction study to assess the effect of NIR/r on the CYP3A substrate midazolam (Study 1013) is currently ongoing. DDI recommendations in the EUA Factsheet are generally aligned with the ritonavir and other ritonavir containing drug labels. An additional interaction was added to the Paxlovid EUA Fact Sheet for BIKTARVY (bictegrovir, emtricitabine, tenofovir alafenamide) and clinical recommendations were revised for immunosuppressant drugs and HMG-CoA reductase inhibitors.

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 factsheet 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.

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 has 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 include a timeframe in which patients on simvastatin or lovastatin are eligible for Paxlovid therapy. Specifically, patients should discontinue lovastatin and simvastatin at least 12 hours prior to initiation of Paxlovid.

Effect of other drugs on NIR/r

Despite being co-administered with ritonavir (a potent CYP3A inhibitor), there is potential for strong inhibitors and inducers to alter the pharmacokinetics of NIR. Therefore, clinical drug interaction studies were conducted with itraconazole as strong CYP3A inhibitor and with carbamazepine as a strong CYP3A inducer (see below).

In vitro transporter assays indicated that NIR was a substrate for human MDR1 (P gp), but was not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Study 1015 – Itraconazole DDI

Study 1015 was a Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of a strong CYP3A4 inhibitor, itraconazole, on the PK of NIR/r. In Period 1, subjects received NIR/r 300/100 mg orally q12h for a total of 5 doses, with the last dose administered on the morning of Day 3. In Period 2, subjects received itraconazole 200 mg orally q24h for 8 days. On Days 4 through 6 of Period 2, subjects received NIR/r 300/100 mg orally q12h for a total of 5 doses.

Overall, NIR mean AUC_{tau} and C_{max} increased by approximately 39% and 19% respectively, when NIR/r was co-administered with itraconazole compared of NIR/r administered alone **Table 23**. Itraconazole had minimum effect on the overall systemic exposure of ritonavir with a 21% and 15% increase in ritonavir exposure (AUC_{tau} and C_{max}, respectively) observed in the presence of itraconazole. Mean t_{1/2} values for ritonavir were 5.72 hours when NIR/r administered alone versus 7.65 hours when co-administered with itraconazole.

Table 23. Study 1015 Plasma Nirmatrelvir and Ritonavir Plasma PK Parameters

	NIR (suspension)/r 300/100 mg BID	Itraconazole 200 mg QD + NIR(suspension)/r 300/100mg BID
Nirmatrelvir Plasma PK Parameters		
AUC _{tau} (µg.hr/mL)	33.35 (20)	46.29 (18)

AUC _{last} (µg.hr/mL)	41.84 (21)	74.43 (21)
C _{max} (µg/mL)	4.68 (17)	5.55 (15)
t _{1/2} (hr)	8.26 ± 1.95	7.80 ± 0.89
T _{max} (hr)	1.02 (0.50-2.08)	1.70 (0.50-4.00)
Ritonavir Plasma PK Parameters		
AUC _{tau} (µg.hr/mL)	7.19 (30)	8.69 (31)
AUC _{last} (µg.hr/mL)	7.84 (33)	10.23 (37)
C _{max} (µg/mL)	1.44 (23)	1.65 (29)
t _{1/2} (hr)	5.72 ± 1.24	7.65 ± 1.63
T _{max} (hr)	1.57 (1.47-3.98)	1.98 (1.47-3.98)

This increase in NIR exposure is not expected to result in additional safety concerns given NIR was well tolerated in healthy adult subjects at supratherapeutic exposures (See *Section XI. Human Clinical Safety*). Thus, no dose adjustment is recommended when Paxlovid is used concomitantly with strong CYP3A4 inhibitors.

Study 1014 – Carbamazepine DDI

Study 1014 was a Phase-1, open label, fixed sequence, 2 period crossover study to estimate the effect of a strong CYP3A4 inducer, carbamazepine, on the PK of NIR and ritonavir in healthy subjects.

In Period 1, subjects received a single oral dose of NIR/r 300/100 mg. In Period 2, subjects received carbamazepine in a titrated schedule as follows: On Days 1-3 carbamazepine 100 mg BID, Days 4-7 carbamazepine 200 mg BID, and on Days 8-15 carbamazepine 300 mg BID. On Day 14, a single dose of NIR/r 300/100 mg was administered.

The effect of multiple dose carbamazepine was significantly greater on ritonavir PK as compared to NIR. Following multiple dose co-administration with carbamazepine as compared to dosing of NIR/r alone, NIR mean AUC_{inf} and C_{max} values decreased by approximately 55% and 43% respectively while ritonavir AUC_{inf} and C_{max} values decreased approximately 83% and 74%, respectively.

Table 24. Study 1014: Plasma Nirmatrelvir and Ritonavir Plasma PK Parameters

	NIR 300/ritonavir 100 mg	Carbamazepine + NIR 300/ritonavir 100 mg
Nirmatrelvir Plasma PK Parameters		
AUC _{inf} (µg.hr/mL)	23.01 (23)	10.28 (58)
AUC _{last} (µg.hr/mL)	22.45 (23)	10.05 (58)
C _{max} (µg/mL)	2.21 (33)	1.30 (43)
t _{1/2} (hr)	6.05 ± 1.79	3.85 ± 0.99
T _{max} (hr)	3.0 (1.02 – 6.00)	1.50 (0.50 - 4.00)
Ritonavir Plasma PK Parameters		
AUC _{inf} (µg.hr/mL)	3.60 (47)	0.68 (61)
AUC _{last} (µg.hr/mL)	3.41 (47)	0.47 (104)

C _{max} (µg/mL)	0.36 (46)	0.10 (71)
t _{1/2} (hr)	6.15 ± 2.24	3.35 ± 0.80
T _{max} (hr)	3.98 (1.48 -4.20)	1.98 (0.98 – 4.00)

Based on these study results, Paxlovid is contraindicated with potent CYP3A4 inducers like carbamazepine where significantly reduced NIR/r plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Due to the delayed offset of induction, additional language was added in the factsheet to alert prescribers against the immediate use of Paxlovid following discontinuation of contraindicated CYP3A inducers. The time course for CYP3A enzymes to return to normal activity precludes the use of Paxlovid in these patients.

Patients on ritonavir- or cobicistat-containing HIV or HCV regimens

In Study 1015, NIR geometric mean AUC_{tau} increased 39% when NIR was coadministered with RTV vs itraconazole plus RTV. Based on the results of this study, no significant increase in NIR exposures are expected when additional CYP3A inhibitors (such as cobicistat or additional doses of ritonavir) are co-administered with NIR/r. This increase in exposure is well below what was noted with the suprathreshold NIR 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.

XII. Nonclinical Data to Support Safety

Genotoxicity studies with nirmatrelvir

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

Safety pharmacology findings with nirmatrelvir

Safety pharmacology studies with NIR 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 NIR to male rats produced no effects on functional observatory behavior (FOB) parameters, but NIR (at 1000 mg/kg) administration resulted in transient locomotor effects, as evidenced by 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 NIR also resulted in transient respiratory effects (higher respiratory rate and minute volume) compared to vehicle control animals. These central nervous system (CNS) and respiratory effects occurred at systemic exposures approximately 12 times higher than clinical exposure at the authorized human dose of Paxlovid.

Several in vitro assays were conducted to assess for potential effects of NIR on cardiovascular function. In a hERG assay, the IC₅₀ for NIR on hERG potassium current was estimated to be greater than 300 µM. In a guinea pig isolated Langendorff-perfused heart model, NIR did not produce a statistically significant change in cardiac function (+dP/dT, LVP, CPP) or cardiac conduction (PR, QRS, QT intervals) at any of the concentrations tested (0.03 µM-100 µM). NIR did not produce a vasoconstriction response in the rat isolated aorta tissue bath preparation (EC₅₀ value >100 µM).

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 NIR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. NIR 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). NIR-related cardiovascular findings in monkeys were observed at systemic exposure about 2 times higher than clinical exposure at the authorized human dose of Paxlovid.

The potential effects on CNS, cardiovascular and respiratory safety pharmacology parameters are monitorable in the clinic and 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 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.

Hematology findings in rats and monkeys with nirmatrelvir

In an oral 14-day repeat dose toxicology study with NIR in rats, there were dose-dependent prolongations in prothrombin time (PT) in males at ≥60 mg/kg/day (16-150%) and females at 1000 mg/kg/day (40%), and prolongations in activated partial thromboplastin time (APTT) in males at ≥200 mg/kg/day (9-19%) and females at 1000 mg/kg/day (11%) with no clinical or microscopic correlates. The mechanism for the prolongations in PT and APTT is unclear but indicates alterations in the coagulation pathway. Platelet counts were also higher (22-25%) at 1000 mg/kg/day in both sexes. In females administered 1000 mg/kg/day, reduced red blood cell (RBC) counts, hematocrit (HCT) and hemoglobin (HGB) (4-5%) and higher (10%) fibrinogen (FIB) were observed. At 200 mg/kg/day, where NIR-related PT and APTT prolongation were noted, the systemic NIR exposure in rats was about 1.2 times higher than clinical exposure at the authorized human

dose of Paxlovid. All of the hematology and coagulation findings had no clinical or microscopic correlations, and all findings were completely recovered at the end of the recovery phase. Therefore, these findings are not considered adverse, and the No-Observed-Adverse-Effect-Level (NOAEL) was the high dose of 1000 mg/kg/day, resulting in systemic exposure (AUC₂₄) in rats about 4 times higher than clinical exposure at the authorized human dose of Paxlovid.

In an oral 15-day repeat dose toxicology study with NIR in cynomolgus monkeys, an increase (72-109%) in FIB, compared with baseline, was observed in 2 of 3 males and 1 of 3 females administered 600 (300 BID) mg/kg/day. Since no relevant clinical or histopathological findings correlated to the increase in FIB, the NOAEL was the high dose of 600 (300 BID) mg/kg/day. At this dose level, the systemic exposure in monkeys was about 18 times higher than clinical exposure at the authorized human dose of Paxlovid.

Liver and thyroid findings in rats with nirmatrelvir

In the oral 14-day repeat dose toxicology study in rats, minimal to mild periportal hepatocellular hypertrophy in females at ≥ 200 mg/kg/day and in males at 1000 mg/kg/day with concomitant increased incidence and severity (minimal to mild) of periportal hepatocyte vacuolation in females at 1000 mg/kg/day were noted in the liver and were associated with higher (35-59%) mean liver weights and macroscopic liver finding of abnormal size (enlarged) in males and females at 1000 mg/kg/day. The hepatocellular hypertrophy was consistent with microsomal enzyme induction. In addition, thyroid follicular cell hypertrophy (minimal to mild) was noted in males and females at 1000 mg/kg/day and was characterized by increased size of follicular cells. Effects in thyroid was most likely due to increased thyroid hormone clearance secondary to hepatocellular enzyme induction, a mechanism that rats are known to be particularly sensitive to relative to humans.

In the recovery phase, there were no test article-related organ weight differences in the liver in males and/or females. Microscopic changes had completely recovered as there were no test article-related microscopic findings in the liver and/or thyroid gland at ≥ 200 mg/kg/day indicating full recovery of the effects on these organs at 1000 mg/kg/day.

Both the liver and thyroid findings were considered non-adverse based on their low severity and the absence of microscopic evidence of associated tissue damage or correlating alterations in clinical pathology parameters. The dose level of 200 mg/kg/day, at which minimal hepatocellular hypertrophy was noted, resulted in systemic exposure in rats about 1.2 times higher than the clinical exposure at the authorized human dose of Paxlovid. The highest dose of 1000 mg/kg/day is considered NOAEL. At this dose level, the systemic exposure in rats was about 4 times higher than clinical exposure at the authorized human dose of Paxlovid.

Developmental and Reproductive effects with nirmatrelvir

- Fertility and early embryo developmental study in rats

In a fertility and early embryo developmental (FEED) study, male and female rats were orally administered 60, 200, or 1000 mg/kg/day of NIR beginning 14 days prior to mating (i.e., treated males and females were mated together), throughout the mating phase, and continued through gestation day (GD) 6 for females and for a total of 32 doses for males. No NIR-related effects on male systemic toxicity or NIR-related 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 NIR-related effects on estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations were observed. Based on the lack of NIR-related adverse effects, the NOAEL for male and female fertility (and systemic toxicity) was 1000 mg/kg/day. At this dose level, the systemic exposure in rats was approximately 4 times higher than clinical exposure at the authorized human dose of Paxlovid. (AUC values in this FEED study were not reported. AUC₂₄ was estimated based on the 14-day repeat dose toxicology study.

- Embryo and fetal developmental effects in rats and rabbits

In an embryo-fetal developmental study (EFD) in rats, NIR was administered orally at doses up to 1,000 mg/kg/day during organogenesis (on GD 6 through 17). No NIR-related maternal effects were observed. In addition, no NIR-related effects on fetal body weights or fetal external, visceral, or skeletal morphology were observed. Based on the lack of NIR-related adverse effects in this study, the maternal and developmental NOAEL was the high dose of 1000 mg/kg/day. At this dose level, the systemic exposure in rats was about 8 times higher than clinical exposure at the authorized human dose of Paxlovid.

In an EFD study in rabbits, NIR was administered orally at doses up to 1,000 mg/kg/day during organogenesis (on GD 6 through 19). NIR-related lower (9%) fetal body weight was observed at the high dose (1000 mg/kg/day). No NIR-related maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology were observed. Based on the lack of NIR-related adverse maternal toxicity, the maternal NOAEL was 1000 mg/kg/day. There were also no NIR-related effects on fetal viability or morphological development in the study. However, the NOAEL for developmental toxicity was 300 mg/kg/day based on lower fetal body weights at 1000 mg/kg/day. At 1,000 mg/kg/day, the systemic exposure (AUC₂₄) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose of Paxlovid. At 300 mg/kg/day, the systemic exposure in rabbits was about 3 times higher than the clinical exposure at the authorized human dose of Paxlovid.

- Pre- and postnatal developmental study in rats (unaudited interim study report)

An interim report of an ongoing pre- and postnatal developmental (PPND) study in rats including data up to postnatal day (PND) 56 of the F1 offspring was reviewed. In this study, rats were administered NIR orally at doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20. No adverse 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). Based on this preliminary data, the NOAEL was identified at 1000 mg/kg/day. The maternal systemic exposure (AUC₂₄) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of Paxlovid (PK data are not available in this interim report. Drug concentrations in maternal and offspring plasma and breastmilk were not reported and so exposure multiples were estimated based on rat AUC₂₄ in the 28-day repeat dose toxicology study). No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure (AUC₂₄) approximately 5 times higher than clinical exposures at the authorized human dose of Paxlovid.

Developmental and Reproductive effects with ritonavir

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of Paxlovid. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of Paxlovid. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of Paxlovid. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the authorized human dose of Paxlovid, based on a body surface area conversion factor. In pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of Paxlovid, based on a body surface area conversion factor.

XIII. Nonclinical Data to Support Efficacy

Mechanism of Action

NIR is a reversible competitive inhibitor of the SARS-CoV-2 Main protease (Mpro), also referred to as the 3C-like protease (3CLpro) or nsp5 protease. NIR inhibits the Mpro by binding directly to the active site, forming a covalent bond with the catalytic residue (Cys145) and non-covalent interactions with ten other residues. Mpro inhibition prevents proteolytic processing of the pp1a/pp1ab polyproteins, a critical early step in the viral replication cycle. The mechanism of action of NIR as an Mpro inhibitor is supported by data from biochemical, cell culture, and animal studies.

Summary of Data Reviewed for Nonclinical Virology-Related Studies

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, NIR inhibited the activity of a recombinant SARS-CoV-2 (Wuhan-Hu-1) Mpro with an IC₅₀ value of 19.2 nM and a K_i value of 3.1 nM. NIR also inhibited recombinant Mpro enzymes from other human coronaviruses (SARS-CoV-1, MERS-CoV, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63), with IC₅₀ values ranging from 28.9 to 479 nM.
- NIR was found to bind to the active site of the SARS-CoV-2 (Wuhan-Hu-1) Mpro by X-ray crystallography. The structure shows that NIR covalently binds to the Mpro catalytic residue C145. NIR also forms non-covalent interactions with ten other residues: H41, M49, F140, G143, H163, H164, M165, E166, L167, and P168. Twelve additional residues are located within 5 Å but do not directly contact NIR: Y54, L141, N142, S144, H172, V186, D187, R188, Q189, T190, A191, and Q192.
- These 23 residues of the SARS-CoV-2 Mpro, which directly interact with or are located in close proximity of NIR, were found to be highly conserved in SARS-CoV-2 (GISAID; ~3.8 million sequences; accessed 12/5/2021), with substitution frequencies ≤0.1%.
- In cell culture antiviral activity studies, NIR had anti-SARS-CoV-2 activity in differentiated normal human bronchial epithelial (dHNBE, EC₅₀ value: 32.6-61.8 nM), A549-ACE2 (EC₅₀ value: 77.9 nM), and Vero E6 (EC₅₀ value: 4480 nM) cells. Antiviral activity was weaker in Vero E6 cells due to a high level of P-gp expression. In the presence of a P-gp inhibitor (CP-100356), NIR had an ~60-fold lower EC₅₀ value of 74.5 nM in Vero E6 cells, similar to the EC₅₀ values observed in the other cell types. The lower level of P-gp expression in A549-ACE2 and dHNBE 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).
- NIR retained activity (≤3-fold change in susceptibility) against five SARS-CoV-2 variants: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and C.37 (Lambda). No reduction in activity was observed against B.1.617.2 (Delta, EC₅₀ fold-change <1). Only B.1.351 (Beta) had reduced susceptibility across all assay formats (2.9-fold higher EC₅₀ value on average). No data are available regarding the activity of NIR against the B.1.1.529 (Omicron) variant in cell

culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce NIR activity (K_i fold change <1) compared to the Wuhan-Hu-1 enzyme.

- NIR also had activity against SARS-CoV-1 in Vero E6 cells (EC_{50} value: 151 nM with P-gp inhibitor), MERS-CoV in Vero 81 cells (EC_{50} value: 166 nM with P-gp inhibitor), and HCoV-229E in MRC-5 cells (EC_{50} value: 190 nM). Thus, NIR appears to have broad anti-CoV activity. NIR did not have activity against enterovirus 71 or human rhinovirus 1B, which encode 3C proteases structurally similar to CoV Mpro. These results indicate that the antiviral activity of NIR is limited to coronaviruses.
- Ritonavir, an HIV-1 protease inhibitor with pharmacokinetic enhancing activity, had no activity against SARS-CoV-2 in cell culture. In addition, ritonavir did not significantly antagonize the activity of NIR against SARS-CoV-2 in cell culture.
- NIR 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 sponsor selected a NIR target plasma exposure (C_{trough}) 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).

Assessments of Cytotoxicity and Off-Target Activity

- NIR had low cytotoxicity in A549-ACE2 (CC_{50} value >3 μ M), Vero E6 (CC_{50} value >100 μ M), Vero 81 (CC_{50} value >100 μ M), and MRC-5 (CC_{50} value >100 μ M) cells used in antiviral activity studies, reflecting favorable selectivity indices of >22 to >1342 across different experiments.
- In biochemical assays, NIR did not inhibit 8 mammalian proteases (IC_{50} value >100 μ M or >10 μ M), including 3 cysteine proteases. In addition, NIR did not inhibit HIV-1 protease (IC_{50} value >100 μ M).

Resistance Development and Cross-Resistance

- Biochemical assays using recombinant SARS-CoV-2 Mpro identified 10 substitutions that led to reduced activity (≥ 3 -fold higher K_i values) of NIR: G15S (4.4-fold), Y54A (23.6-fold), T135I (3.5-fold), F140A (39.0-fold), S144A (91.9-fold), H164N (6.4-fold), E166A (33.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). C.37 (Lambda) contains G15S and did not have reduced susceptibility to NIR in cell culture (EC_{50} fold-change <1). The impacts of the other substitutions have not been tested in cell culture.
- Preliminary cell culture resistance selection studies with NIR using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The presence of the substitutions P55L and S144A was associated with reduced NIR susceptibility (~ 4 -5-fold higher EC_{50} values);

these positions correspond to E55 and S144, respectively, in the SARS-CoV-2 Mpro. E55L alone did not affect NIR activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A led to significantly reduced NIR activity (91.9-fold higher K_i value on average). Neither substitution has been tested in SARS-CoV-2 in cell culture.

- Cross-resistance is not expected between NIR and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

Activity in Animal Models of SARS-CoV-2 Infection

NIR was shown to have antiviral activity in 129 or BALB/c mice infected with mouse-adapted (MA) SARS-CoV-2 MA10. In these studies, NIR dosing modeled a post-exposure prophylaxis and not a treatment of symptomatic disease. SARS-CoV-2 MA10 does not encode any Mpro substitutions relative to SARS-CoV-2.

- In 129 mice, NIR was administered PO at 300 or 1000 mg/kg BID, beginning 4 or 12 hours post-infection and continuing until the termination of the study 3 days post-infection. At 1,000 mg/kg, NIR reduced lung virus titers by $\sim 4 \log_{10}$ and lung histopathology at 3 days post-infection.
- In BALB/c mice, NIR was administered PO at 300 or 1000 mg/kg BID, beginning 4 hours post-infection and continuing until the termination of the study 4 days post-infection. NIR reduced lung virus titers by $\sim 1.4 \log_{10}$ or $\sim 1.9 \log_{10}$ at 300 or 1,000 mg/kg, respectively, at 4 days post-infection. NIR also resulted in decreased SARS-CoV-2 N protein staining in lungs. Lastly, NIR prevented weight loss and led to dose-dependent reductions in lung histopathology at 4 days post-infection.

Nonclinical/Clinical Resistance Summary

The following table provides a comprehensive summary of currently available nonclinical and clinical data characterizing potential NIR resistance pathways.

Table 25. Summary of available nonclinical and clinical analyses of potential NIR resistance pathways.

Mpro AA Position (SARS-CoV-2 numbering)	NIR Contact?	Position of Interest (X) ¹	Substitution (Rel. to Wuhan-Hu-1)	FC in Activity Mpro Biochemical Assay	FC in Activity SARS-CoV-2 in Cell Culture	Emerged in NIR-selected MHV in cell culture	Emerged in NIR-selected SARS-CoV-2 in cell culture	Emerged in NIR/r Treated Subjects
15	No	X	G15S	4.36	0.86 (Lambda) ²	Yes (P15A)		
17	No		G17S	1.55				
41	Yes	X	H41Y					
45	No		T45I	1.97				
49	Yes	X	M49I	<0.86				
50	No	X	L50	Not tested		Yes (T50K)		
54	Yes	X	Y54A	23.6	In progress			
55	No	X	E55L	<0.51	In progress	Yes (P55L)		
70	No		A70T	<0.37				
75	No		L75F	0.63				
83	No		Q83K	1.88				
88	No		K88R	0.47				

89	No		L89F	1.32			
90	No		K90R	1.13	2.93 (Beta) ²		
96	No		V96I	<0.74			
108	No		P108S	2.78			
129	No	X	A129	Not tested		Yes (T129M)	
132	No		P132H	0.69	In progress (Omicron) ²		
			P132L	1.07			
			P132S	0.6			
135	No	X	T135I	3.46			
140	Yes	X	F140A	39	In progress		
141	Yes	X	L141I/F	Not tested			
142	Yes	X	N142L	1.1			
			N142S	<0.72			
143	Yes	X	G143S	2.54			
144	Yes	X	S144A	91.9	In progress	Yes (S144A)	
145	Yes	X	C145F				
			C145I				
163	Yes	X	H163A				
164	Yes	X	H164N	<6.41 (??)			
165	Yes	X	M165I	<1.11			
166	Yes	X	E166A	33.4	In progress		
167	Yes	X	L167I	2.5			
168	Yes	X	P168R	2.59			
			P168S	0.88			
172	Yes	X	H172Y	233	In progress		
186	Yes	X	V186F/I	Not tested			
187	Yes	X	D187Y	Not tested			
188	Yes	X	R188K/S	Not tested			
189	Yes	X	Q189K	65.4	In progress		
190	Yes	X	T190A	0.56			
			T190I	0.64			
191	Yes	X	A191T	<2.84			
			A191V	<1.26			
192	Yes	X	Q192K/L	Not tested			
212	No		V212F	0.72			
213	No		I213L	0.47			
220	No		L220F	<1.66			
234	No		A234V	2.52			
248	No	X	D248E	3.65			
252	No		P252L	<0.84			
253	No		L253V	<0.63			
260	No	X	A260T	Not tested			Yes
			A260V	0.53			Yes
266	No		A266V	2.27			
Footnotes				Color coding for phenotype data		Color-coding for emergence data	
1. Criteria for flagging: in/near NIR binding site, phenotypic fold-change ≥3, or emerged in nonclinical or clinical studies				Fold-change <3 from WT		Emerged in clinical trial C4671005 (in at least 2 NIR/r-treated subjects and relative to PBO-treated subjects), or	
				Fold-change 3-10x from WT			
2. Substitutions tested in context of authentic virus isolates representative of noted variant.				Fold-change >10x from WT		Emerged in NIR-selected MHV or SARS-CoV-2 in cell culture studies	
				Tested but no data due to inactive enzyme/virus			

XIV. Supply Information

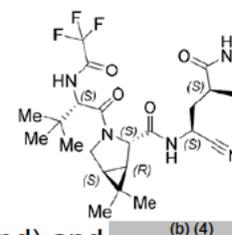
One treatment course of Paxlovid per individual for the proposed EUA consists of 300 mg NIR (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. Therefore one treatment course is supplied as 20 NIR tablets and 10 ritonavir tablets. A reduced dosage is recommended for patients with moderate renal impairment (one 150 mg tablet NIR with one 100 mg tablet ritonavir taken together orally twice daily for 5 days).

On December 20, 2021 Pfizer provided updated supply projections for Paxlovid to increase the projection for the first half of 2022 from (b) (4) – for the global supply. Increases are projected for the more immediate (b) (4) US supply in order to bring forward the target date 10 million doses to the US from (b) (4) (table below).

Packs, By Month (k)	Total	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Current US Commitment	10,000	(b) (4)												
Changes Needed to Achieve 10M July	-0-	(b) (4)												
Revised US Schedule	10,000	(b) (4)												

XV. Chemistry, Manufacturing, and Controls Information

Nirmatrelvir contains six stereocenters and has low solubility (0.90-1.21 mg/mL) across the physiologically relevant pH range. Critical stereochemical and solid state characteristics are controlled during the manufacturing process and the drug substance specification. The drug substance manufacturing process has undergone development and two manufacturers were proposed for this EUA: Pfizer Ireland (Ringaskiddy, Ireland) and (b) (4)



(b) (4). Pfizer Ringaskiddy manufactured initial EUA supplies using (b) (4) and will be using a slightly modified route – (b) (4) – moving forward. (b) (4) is manufacturing emergency supplies using (b) (4). Synthetic (b) (4) are comprised of the same (b) (4).

The batch data for (b) (4) and (b) (4) drug substance were comparable. The totality of the information provided in the EUA, including the comparability of these batch data, is adequate to support the manufacture of nirmatrelvir drug substance for emergency supply at Pfizer Ringaskiddy using (b) (4), and at (b) (4) using (b) (4). The specifications for (b) (4) and (b) (4) drug substance are adequate to ensure the identity, strength, and purity of nirmatrelvir drug substance. Adequate safety justification was provided for the specified impurities controlled at levels above the ICH Q3A qualification threshold (per consult with Nonclinical Reviewer Dr. Z. Li). The remaining specified impurities and unspecified impurities are controlled at the ICH Q3A qualification threshold (0.15%) and identification threshold (0.10%), respectively. Sufficient theoretical purge factors were provided to justify ICH M7 Option 4 control of the (b) (4) identified potential mutagenic impurities. Data provided supported a 12-month retest period for nirmatrelvir drug substance for emergency supply. The totality of the CMC information provided for nirmatrelvir drug substance in the EUA is adequate to support authorization of the EUA from a drug substance perspective.

The drug product contains co-packaged 150 mg nirmatrelvir tablets and 100 mg ritonavir tablets. For the EUA supplies, nirmatrelvir tablets and ritonavir tablets are contained within individual cavities of the aluminum foil/foil blisters with a child-resistant PET layer. Each carton contains one blister card for each of the five dosing days, divided into morning and evening doses. CMC information for nirmatrelvir tablets was submitted in EUA 105 and for the ritonavir tablets is referenced to NDA 22417 for Norvir (ritonavir) tablets. Each nirmatrelvir tablet is 8.5 x 17.5 mm oval-shaped debossed (PFE and 3CL), and weighs (b) (4) mg. Each tablet contains 150 mg nirmatrelvir, (b) (4) mg MCC (b) (4), (b) (4) mg lactose (b) (4), (b) (4) mg croscarmellose sodium (b) (4), (b) (4) mg silicon dioxide (b) (4), (b) (4) mg sodium stearyl fumarate (b) (4) and (b) (4) mg (b) (4) (film coat). The proposed emergency use supply for nirmatrelvir tablets will be manufactured using a (b) (4) process comprised of (b) (4)

(b) (4). The totality of the data from the registration batches, stressed ASAP studies, forced degradation studies and the demonstrated intrinsic stability of the nirmatrelvir drug substance support the proposed 12-month expiry period for nirmatrelvir tablets. Ritonavir tablets have a marketing history of storage in less protective containers, therefore a 12-month expiry for the co-package drug product was found acceptable.

Initially Pfizer proposed that all labeling refer to nirmatrelvir tablets as PF-07321332 tablets. Nomenclature updated as 'nirmatrelvir' was adopted by USAN on November 24, 2021.

XVI. Manufacturing Site Inspections

Table 26: Manufacturing Sites

Manufacturing Site Identifier	Drug Substances / Intermediates/ Drug Product / Testing /Labeler / Packager	Location (U.S. and Non-U.S.)	Inspection Dates	GMP Status (if Known)
Pfizer Ireland Pharmaceuticals, FEI 3002807852 (b) (4)	Nirmatrelvir drug substance (DS) manufacturing and testing	Cork, Ireland	Aug2018 ¹	Acceptable
(b) (4)	Nirmatrelvir drug substance (DS) manufacturing and testing	(b) (4)	(b) (4)	Acceptable
Pfizer Manufacturing Deutschland GmbH, FEI 3002807097	Nirmatrelvir drug product (DP) manufacturing and testing, Co-packaging of Nirmatrelvir DP and Ritonavir DP	Freiburg, Germany	Feb2020	Acceptable

(b) (4)	Co-packaging of Nirmatrelvir DP and Ritonavir DP	(b) (4)	Acceptable
Pfizer Inc., FEI 3003836868	DP Stability testing	NJ, U.S.	Jun2016 ³ Acceptable
(b) (4)	Ritonavir DS manufacturing	(b) (4)	Acceptable
	Ritonavir DP manufacturing		Acceptable

¹ FDA evaluated an inspection of Pfizer Ireland Pharmaceuticals, FEI 3002807852 conducted by the The Health Products Regulatory Authority of Ireland from August 13, 2018 to August 17, 2018 under the Mutual Recognition Agreement and determined the inspection classification of this facility is VAI. This facility was last inspected by the FDA from January 22, 2018 to January 26, 2018 and the inspection classification of this facility was VAI.

² (b) (4) was last inspected by FDA from (b) (4) and the inspection classification of this facility was NAI. Subsequently, the FDA conducted a remote regulatory assessment from (b) (4) and did not find any significant issues.

³ Pfizer Inc., FEI 3003836868 was last inspected by FDA from June 1, 2016 to June 2, 2016 and the inspection classification of this facility was NAI. Subsequently, the FDA conducted a remote regulatory assessment from January 8, 2021 to March 31, 2021 and did not find any significant issues.

⁴ (b) (4) was last inspected by FDA from (b) (4) and the inspection classification of this facility was VAI. Subsequently, the FDA conducted a remote regulatory assessment from (b) (4) and did not find any significant issues.

Abbreviations: DP, drug product; DS, drug substance; EUA, emergency use authorization; GMP, good manufacturing practice; OAI, official action indicated; U.S., United States

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to protect the public health⁷:

- The Sponsor will manufacture Paxlovid to meet all quality standards and per the manufacturing process and control strategy as detailed in the Sponsor's EUA request. The Sponsor will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.
- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).
- The Sponsor will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of Paxlovid that includes the following:
 - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or

⁷ See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #622919, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated December 20, 2021, associated with EUA 105.

- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Pfizer must recall them.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- The Sponsor will list Paxlovid (NIR tablets co-packaged with ritonavir tablets) with a unique product National Drug Code under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

XVII. Clinical Trial Site Inspections

Clinical trial site inspections were not conducted for this EUA.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

The following COVID-19 treatment guidelines recommend using SARS-CoV-2 spike protein-directed attachment inhibitors bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab (alone) for the treatment of patients with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19:

- The National Institutes of Health (NIH) COVID-19 Treatment guidelines (<https://www.covid19treatmentguidelines.nih.gov/outpatient-management/>; updated October 19, 2021). The rating of the recommendation and the rating of evidence vary based on the population from AllA (strong recommendation based on other randomized trials or subgroup analyses of randomized trials) to BIII (moderate recommendation based on expert opinion).
- The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 (<https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and->

[management](#); updated November 18, 2021). The strength of recommendation is rated weak or conditional. The certainty of evidence is rated moderate.

Paxlovid is not currently included in COVID-19 treatment guidelines as it is currently not approved nor authorized for emergency use in the United States.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Paxlovid (NIR/r) is an oral antiviral medication developed for the treatment of COVID-19. Paxlovid is comprised of NIR, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of NIR and consequently increase NIR plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. Paxlovid will be administered as two 150 mg tablets of NIR and one 100 mg tablet of ritonavir all given orally twice a day for five days in most authorized populations (a lower dose will be recommended for patients with moderate renal impairment).

Based on FDA's review of the totality of scientific evidence available, including data from EPIC-HR (NCT04960202), a randomized, double-blind, placebo-controlled Phase 2/3 trial of Paxlovid administered to symptomatic non-hospitalized adults with documented SARS-CoV-2 infection who were at high risk for progression to severe COVID-19, it is reasonable to believe that Paxlovid may be effective for use as 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. FDA has also determined that the known and potential benefits of Paxlovid, when used for the treatment of mild-to-moderate COVID-19 as described in *Section III* of this memorandum, outweigh the known and potential risks of the product.

The primary endpoint for EPIC-HR was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The primary analysis population included only subjects who were dosed within 3 days of symptom onset and who had not received or were not expected to receive COVID-19 monoclonal antibody products.

EPIC-HR Interim Analysis

The initial EUA submission contained data from the interim analysis (n=1,361) where event rates for the primary endpoint in the primary analysis population were 0.8% in the Paxlovid group versus 7.0% in the placebo group. Paxlovid treatment resulted in a 6.3% (95% CI: -9.0% to -3.6%; p<0.0001) absolute reduction, or 89.1% relative reduction, compared to placebo for COVID-19 related hospitalization or death from any cause through Day 28. The difference was highly statistically significant and met the pre-specified stopping boundary leading to the E-DMC's recommendation to stop enrollment.

Secondary and supportive analyses also demonstrated a benefit with Paxlovid treatment in the interim analysis. A secondary analysis in the population which included subjects who were dosed within 5 days of symptom onset and who had not received or were not expected to receive COVID-19 mAb products, showed similar results to the primary analysis: event rates were 1.0% in the Paxlovid group versus 6.6% in the placebo group. In this population, Paxlovid treatment resulted in a 5.7% (95% CI: -7.9% to -3.6%; $p < 0.0001$) absolute reduction, or 85.3% relative reduction, compared to placebo for COVID-19 related hospitalization or death from any cause through Day 28. Results were also similar in the population which included subjects who were dosed within 5 days of symptom onset regardless of mAb antibody treatment, with event rates of 1.0% in the Paxlovid group versus 6.4% in the placebo group (83.6% relative reduction). In addition, all 10 deaths in the interim analysis occurred in the placebo group. Change from baseline in SARS-CoV-2 viral RNA shedding at Day 5 also favored the Paxlovid group, with an additional average reduction of approximately 0.9 log₁₀ copies/mL in the Paxlovid group versus the placebo group among subjects dosed within 5 days of symptom onset who had not received or were not expected to receive COVID-19 monoclonal antibody products.

EPIC-HR Full Topline Analysis

Topline efficacy data from all enrolled and dosed subjects in EPIC-HR (n=2,246), submitted at the end of the EUA review cycle, support the findings from the interim analysis. Treatment with Paxlovid resulted in 88.9%, 87.8%, and 86.7% relative risk reductions for COVID-19 hospitalization or all cause death through Day 28 in subjects dosed within 3 days of symptom onset who did not receive COVID-19 mAb products (mITT population), subjects dosed within 5 days of symptom onset who did not receive COVID-19 mAb products (mITT1 population), and subjects dosed within 5 days of symptom onset regardless of COVID-19 mAb product receipt (mITT2 population), respectively. The EUA Paxlovid treatment course recommended for authorization, which should be initiated as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset, is supported by the EPIC-HR efficacy data in the mITT1 population; these mITT1 efficacy data should be included in the EUA Fact Sheet.

Regarding assessment of the known and potential risks of Paxlovid, the most concerning potential risk involves drug-drug interactions. Paxlovid is both a strong CYP3A inhibitor and also a CYP3A substrate. Consequently, drugs that are extensively metabolized by CYP3A may have large increases in exposure when coadministered with Paxlovid, and drugs that induce CYP3A may decrease NIR and ritonavir plasma concentrations and reduce Paxlovid therapeutic effect. To mitigate this risk, the fact sheet for healthcare providers should include a list of drugs that are contraindicated with Paxlovid, as well as a warning and precaution about the risk of severe or serious adverse reactions due to drug interactions, and

Section 7 should include a table of drugs that are contraindicated with Paxlovid or which may have other potentially significant drug interactions with Paxlovid.

The overall safety database for Paxlovid is comprised of 1,116 adult subjects who were randomized to receive Paxlovid at or above the proposed dose and duration: 1,109 from EPIC-HR (672 from the interim analysis) and 7 from the Phase 1 study C4671001. These clinical trials excluded subjects taking concomitant medications that could interact with Paxlovid. Overall, serious or severe adverse events were more common among placebo recipients versus Paxlovid recipients. Adverse events seen more commonly among Paxlovid versus placebo recipients included dysgeusia, diarrhea, hypertension, and myalgia; these adverse events were each reported by $\leq 6\%$ of Paxlovid recipients and should be included in the fact sheets.

The warnings and precautions should also include hepatotoxicity and the risk of HIV-1 resistance development. Hepatotoxicity is included because hepatotoxicity has been seen with ritonavir use; however, hepatotoxicity was not reported at higher rates among Paxlovid versus placebo recipients in EPIC-HR. The risk of HIV-1 resistance development in individuals with uncontrolled or undiagnosed HIV-1 infection relates to ritonavir being an HIV-1 protease inhibitor as well as a potent CYP3A inhibitor; consequently, Paxlovid use in the absence of other HIV-1 antiretrovirals could serve as functional monotherapy and theoretically lead to development of resistance to HIV-1 protease inhibitors. Other warnings and precautions included in the ritonavir label, which were seen with ritonavir dosed at 600 mg bid for long durations (months to years), should not be included in the Paxlovid fact sheets as these safety signals were not observed with Paxlovid use in EPIC-HR and are considered unlikely with the lower 100 mg bid x 5 days ritonavir dosing regimen used with Paxlovid.

Paxlovid (specifically NIR) is expected to retain antiviral activity against SARS-CoV-2 Variants Being Monitored, including Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1), and the Variant of Concern Delta (B.1.617.2 and AY), based on cell culture antiviral activity assays using authentic SARS-CoV-2 isolates. The susceptibility of the recently identified and rapidly expanding Variant of Concern Omicron (B.1.1.529) to NIR has not yet been determined in a cell culture antiviral activity assay. However, preliminary biochemical data using recombinant Mpro enzymes indicate that NIR is likely to retain activity against the Omicron (B.1.1.529) variant.

Nonclinical virology studies indicate NIR may have a low barrier to resistance, with multiple potential resistance pathways. Certain amino acid changes engineered in Mpro positions near the NIR binding site were shown to confer large reductions in NIR susceptibility in biochemical assays. One such change (S144A, conferring a 92-fold reduction in NIR susceptibility) emerged in mouse hepatitis virus (surrogate coronavirus) selected for resistance to NIR in cell culture. Currently the known potential resistance-associated positions in Mpro are highly conserved in published SARS-CoV-2 sequences and FDA is not aware of any circulating variants that may

be resistant to NIR. Furthermore, the FDA review of preliminary viral sequencing data from EPIC-HR did not identify any clear signals of baseline or treatment-emergent resistance in Paxlovid-treated subjects. Nevertheless, the potential for SARS-CoV-2 to develop resistance to Paxlovid must continue to be assessed and carefully monitored at the population level.

In selecting the authorized use, the FDA carefully considered the available clinical data. EPIC-HR, the only efficacy trial for which data are currently available, evaluated a 5-day course of Paxlovid for the treatment of mild-to-moderate COVID-19 in adult patients at high risk for progression to severe COVID-19. However, as the pharmacokinetics of Paxlovid in adolescents (12 years of age and older weighing at least 40 kg) are expected to be similar to those of adults, and as adolescents are also at risk of severe COVID-19, the authorization was expanded to include the adolescent population. Paxlovid has not been studied for treatment of severe or critical COVID-19 in hospitalized patients or for pre-exposure prophylaxis of COVID-19, and no clinical data are available for Paxlovid used as post-exposure prophylaxis. Consequently, Paxlovid should not be authorized for those uses as the benefit of Paxlovid for those uses is unknown. In addition, Paxlovid is not recommended in patients with severe renal impairment or in patients with severe hepatic impairment due to a lack of data on a safe and effective dose in these populations. Because the recommendations based on renal and hepatic function and the extensive list of Paxlovid drug interactions may necessitate complex benefit/risk assessments and medical management decisions, the review team has determined that Paxlovid may only be prescribed by physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

Based on FDA's review of the totality of scientific evidence available, including data from EPIC-HR (NCT04960202), a randomized, double-blind, placebo-controlled Phase 2/3 trial of Paxlovid administered to symptomatic non-hospitalized adults with documented SARS-CoV-2 infection who were at high risk for progression to severe COVID-19, it is reasonable to believe that Paxlovid may be effective for use as 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. FDA has also determined that the known and potential benefits of Paxlovid, when used for the treatment of mild-to-moderate COVID-19 as described in *Section III* of this memorandum, outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory criteria under section 564(c) of the Federal Food, Drug, and Cosmetic Act are met and recommend authorization of an EUA for Paxlovid as described above.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice under EUA. Investigational product will be used in clinical trials conducted under IND. FDA IND safety reporting regulations will apply.

EUA-labeled product will be made available under the EUA. In the setting of a pandemic where practicing physicians will have competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system. The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events occurring during Paxlovid use and considered potentially related to Paxlovid within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheet for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

The Sponsor's plan for distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients, Parents, and Caregivers is as follows:

- Each carton contains a sufficient quantity of PAXLOVID to complete one treatment course.
- The carton has a QR code on it, which directs users to the URL www.COVID19oralRX.com, which will contain a copy of the Letter of Authorization, the authorized Fact Sheets, and any other documents associated with the emergency use of PAXLOVID (e.g., Dear Healthcare Provider Instructions, Dispensing Instructions).
- The fact sheets will include the global URL www.COVID19oralRX.com.

FDA agrees with the plan for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See *Section XXVI. Appendices*)
- Fact Sheet for Patients and Parents/Caregivers (See *Section XXVI. Appendices*)

XXIV. Outstanding Issues/Data Gaps

The EUA for Paxlovid is primarily based on safety and efficacy data through Day 34 from the ongoing study EPIC-HR. The initial data submitted to support the EUA were based on an interim analysis; topline data from all enrolled subjects were submitted at the end of the review period and support the results of the interim

analysis. However, final full results from EPIC-HR remain critical to confirm the initial benefit-risk assessment. Furthermore, an imbalance in adverse events was seen in the renal impairment study, with more adverse events seen in subjects with severe renal impairment, and so additional clinical data on the safe and appropriate Paxlovid dose in patients with severe renal impairment are needed. In addition, final reports from several nonclinical studies are outstanding and further data to evaluate for potential baseline or treatment-emergent NIR virologic resistance are needed. As such, we are requiring that the Sponsor submit the following information as conditions of authorization:

1. Pfizer must conduct cell culture phenotypic analyses of recombinant SARS-CoV-2 viruses or replicons carrying specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies, or polymorphisms emerging in novel SARS-CoV-2 variants. Specific amino acid changes that should be characterized include the following:
 - amino acid changes associated with reduced nirmatrelvir susceptibility in biochemical assays,
 - natural amino acid polymorphisms in Mpro that come in contact with or in close proximity (<5 Å) to bound nirmatrelvir,
 - amino acid changes associated with nirmatrelvir/ritonavir treatment emergence, treatment failure, or prolonged virologic shedding or rebound in clinical trials, and
 - amino acid polymorphisms identified in resistance surveillance analyses.

Amino acid changes in both Mpro and Mpro cleavage sites should be considered in these analyses. Specific amino acid changes of interest for phenotypic characterization in cell culture assays currently include Mpro substitutions Y54A, E55L, F140A, S144A, E166A, H172Y, Q189K, and A260V. When warranted due to technical challenges, alternative approaches to the requested cell culture assays will be considered on a case-by-case basis. Pfizer must submit a preliminary summary report no later than February 28, 2022 for any currently ongoing studies, and at least every 6 months thereafter as additional data accumulate.

2. Pfizer must evaluate the cell culture antiviral activity of nirmatrelvir against an authentic SARS-CoV-2 isolate representative of the Omicron variant. Pfizer must submit a summary report no later than February 28, 2022.
3. Pfizer must conduct studies characterizing potential nirmatrelvir resistance mechanisms in SARS-CoV-2 in cell culture, including selection and genotypic and phenotypic characterization of nirmatrelvir-resistant virus. Pfizer must submit a brief monthly progress report on these studies, a preliminary summary report no later than April 30, 2022, and a final report within 30 days of study completion.
4. Pfizer must complete analyses of SARS-CoV-2 shedding and nucleotide sequencing from the EPIC-HR clinical trial. Viral sequencing analyses should

be conducted for all clinical samples with sufficient viral RNA levels, including samples collected at baseline, on-treatment and post-treatment, to identify and characterize the potential emergence or persistence of amino acid changes associated with PAXLOVID treatment. Pfizer must submit a summary of available data (including analysis-ready datasets) no later than February 28, 2022, and a final report and associated datasets (including analysis-ready datasets and raw fastq NGS data) no later than April 30, 2022.

5. Pfizer will submit the clinical study report containing data from all enrolled subjects in the EPIC-HR clinical trial no later than January 15, 2022.
6. Pfizer will provide results from a 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), with the study protocol submitted no later than March 31, 2022.
7. Pfizer will provide the audited final report of the rat PPND study, *An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats*, no later than April 30, 2022.

XXV. References

Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020 Sep;4(9):653-661. doi: 10.1016/S2352-4642(20)30177-2.

XXVI. Appendices

1. Pharmacometrics Review
2. Fact Sheet for Health Care Providers
3. Fact Sheet for Patients and Parent/Caregivers
4. Dear Health Care Provider Letter

Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of dose evaluation in adults and adolescent patients. The applicant's population PK analyses were verified by the reviewer, with no significant discordance identified.

1.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the PK of NIR (PF-07321332) in healthy adults;
- Evaluate time- and dose-dependent change in PK; and
- Perform PK simulations to support dose recommendation in patients with COVID-19

1.3 Model development

Data

The analyses were based on PK data from the Phase 1 trial C4671001 that evaluated single and multiple dose escalation in healthy adults. Brief descriptions of the study included are presented in **Table 1**. The final NONMEM data file for analysis contained 536 PK observations from 20 subjects with co-administration of NIR oral suspension and ritonavir. The baseline demographics are presented in **Table 2**.

Table 1. Summary of PK Sampling Included in Population PK Analysis

Protocol	Design	N	PF-07321332 Dose Regimen	Plasma PK Sampling
C4671001[2]	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 participants	Up to 78 planned	PART-1 SAD Suspension ^a <ul style="list-style-type: none"> • Cohort 1: 150 mg^b, 1500 mg^b, 750 mg/RTV • Cohort 2: 500 mg^b, 250 mg/RTV, 250 mg/RTV (fed)^c PART-2 MAD Suspension <ul style="list-style-type: none"> • Cohort 3: 75 mg/RTV q12h • Cohort 4: 250 mg/RTV q12h • Cohorts 5 & 6: 500 mg/RTV q12h PART-3 relative bioavailability/food effect ^b <ul style="list-style-type: none"> • SD: 250 mg suspension, 250 mg tablet, 250 mg tablet (fed)^c PART-4 metabolism & excretion ^d <ul style="list-style-type: none"> • SD 300 mg/RTV PART-5 suprathreshold exposures ^d <ul style="list-style-type: none"> • 750 mg/RTV at 0, 2, & 4 hours 	PART-1 SAD: predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 hours PART-2 MAD: predose only on Days 2, 3, 6, & 8; predose, 0.5, 1, 1.5, 2, 4, 6, 8, & 12 hours post-dose on Days 1, 5, & 10; and 16, 24, & 48 hours post-dose on Day 10 PART-3: predose, 0.5, 1, 1.5, 2, 4, 8, 12, 16, 24, & 48 hours PART-4: predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 hours PART-5: predose, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, & 96 hours

PK = pharmacokinetics; MAD = multiple ascending dose; N = number of subjects; q12h = every 12 hours; RTV = ritonavir 100 mg; SAD = single ascending dose; SD = single-dose.

^aIn SAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) received 3 doses of 100 mg of ritonavir at -12, 0, and 12 hours on Day 1.

^bExcluded from Pop PK analysis.

^cHigh-fat, high-calorie meal.

^dData not yet available.

(Source: Applicant's Population PK Report, Table 1)

Table 27. Summary of Baseline Demographics

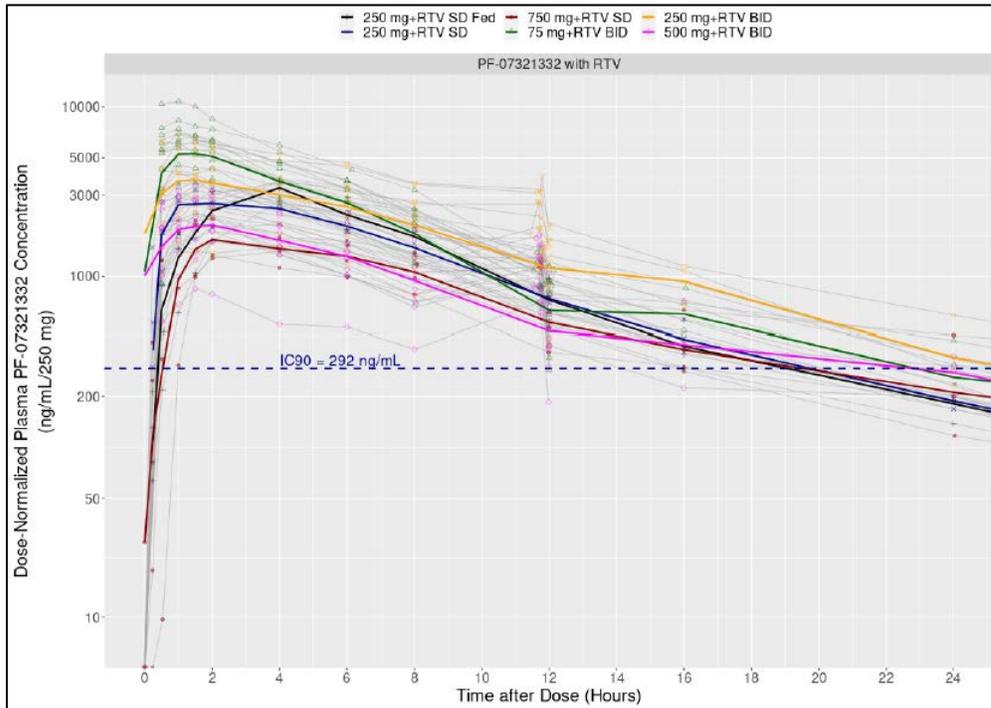
	NIR/r (n=20)
Male, n (%)	16 (44%)
Body weight (kg), median [range]	70.8 [58.5-99.4]
Age (years), median [range]	34.5 [21.0-56.0]
Baseline creatinine clearance (mL/min), median [range]	100 [69.9-141]

(Source: Applicant's Population PK Report, Table 5)

Data visualization

Dose-dependent (less than proportional) absorption was observed (75 to 750 mg) in subjects administered NIR/r (**Figure 1**).

Figure 1. Dose-Normalized NIR Concentration versus Time After Dose for Subjects on NIR/r



BID = twice daily; IC90 = inhibitory concentration 90%; RTV = ritonavir; SD = single dose. Symbols represent individual observations; Light grey lines represent individual profiles; Thick colored lines represent group median profiles; Dashed horizontal blue line represents the target exposure IC90. Excluded observations with time after dose >24 hours.

(Source: Applicant's Population PK Report, Figure 2)

Covariate analysis

Covariate modeling at this stage primarily focused on evaluating dose and food effect on absorption constant (k_a) and relative bioavailability (F_1), and time effect on clearance (CL). Weight was factored using a standard weight allometry (exponent of 0.75 for CL, 1 for V).

Final Model

The PK following oral administration of NIR oral suspension and ritonavir was adequately characterized by a two-compartment disposition model with first-order absorption. The parameter estimates for the final covariate model are listed in **Table 3**.

Table 3. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

	Estimate	% RSE	Shrinkage (%)
CL/F (L/h)	1.02	18.9	
V2/F (L)	8.20	20.8	
Q/F (L/h)	0.444	8.91	
V3 (L)	5.65	20.2	
Weight on CL and Q	0.75 FIX		
Weight on V2 and V3	1 FIX		
k_{a1mg} (1/h)	22.7	4.15	
k_{apower}	-0.533	6.25	
F_{1mg}	1.06	30.5	
F_{1power}	-0.375	16.7	
IIV-CL (% CV)	26.4	29.2	1e-10

COV _{CL-V2}	0.0684	36.0	
IIV-V2 (% CV)	30.7	41.9	5.73
COV _{CL-ka}	0.0582	73.2	
COV _{V2-ka}	0.138	41.4	
IIV-ka (% CV)	54.3	33.6	15.5
COV _{CL-V3}	0.125	58.6	
COV _{V2-V3}	0.0393	152	
COV _{ka-V3}	-0.151	90.5	
IIV-V3 (% CV)	69.9	73.0	7.89
IOV-ka (% CV)	60.7	15.6	38.1; 51.6; 5.23
Proportional error (%)	3.36	111	5.58
Additive error (ng/mL)	399	11.5	5.58

CL = apparent clearance of NIR; Weight effect is parameterized as (Weight/70 kg)^{0.75} on CL and Q, and (Weight/70 kg)¹ on V2 and V3; COV = covariance; F_{1mg} = F1 at 1 mg; F_{power} = exponent of power function for dose effect on F1; IIV = inter-individual variability; IOV = inter-occasion variability; ka = first-order absorption rate constant; ka_{1mg} = ka at 1 mg; ka_{power} = exponent of power function for dose effect on ka; Q = inter-compartmental clearance; %RSE = percent relative standard error; V2 = central volume of distribution; V3 = peripheral volume of distribution

(Source: Applicant's Population PK Report, Table 7)

Reviewer's Comments: The applicant's model is developed using PK data of 20 subjects co-administered NIR oral suspension and ritonavir, fasted or on high fat diet, under various dose scenarios (single dose, multiple doses, dose ranging from 75 to 750 mg). Given that subjects in each combination of the factors are limited, the model is not stable with a large unexplained variability. Because PK data for the final 150 mg IR film-coated tablet formulation from Phase 1 Study 1014 became available late in the review cycle, a comprehensive covariate analysis (for example assessing the effect of formulation [oral suspension vs tablet] on the PK of NIR could not be conducted). While the model is considered preliminary, it identified the impact of dose on bioavailability and absorption rate, which is in accordance with the less than dose proportionality observed. Therefore, the model is acceptable to be used to simulate exposure for COVID-19 patients in the early disease stage, who are assumed to similar to healthy subjects, for assessing dose in adults and pediatrics 12 years and older.

1.4 Simulation

Dose of NIR/r 300/100 mg BID in adults

The applicant applied the population PK model and an inflated IIV in clearance of 60% to simulate exposures for NIR doses of 100 to 500 mg with ritonavir given as BID over 5 days. The C_{12h} and the percentage of subjects achieving a concentration at C_{12h} above EC₉₀ of 292 ng/mL (calculated with in vitro EC₉₀ of 0.181 uM and f_{u,human} of 0.31) are summarized in **Table 4**. The dose of NIR/r 300/100 mg BID results in median Day 1 and steady-state C₁₂ unbound trough concentrations ~3x and ~6x in vitro EC₉₀, respectively.

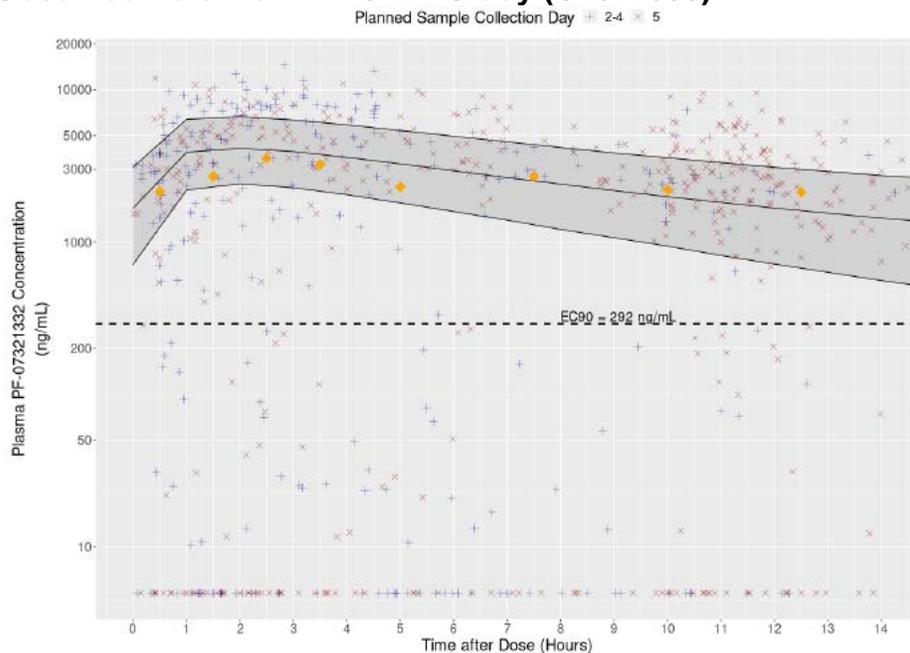
Table 4. Predicted C_{12h} and Percentage of Simulated Subjects Achieving C_{12h} > EC₉₀

Dose (mg) + RTV ^a	Dose Number	C _{12h} (ng/mL)			% Subjects Achieved C _{12h} ≥ IC ₉₀
		Median	10 th percentile	90 th percentile	
100	1 st (Day 1)	458	141	1018	71.5
	2 nd (Day 1)	631	175	1546	79.2
	9 th (Day 5)	852	238	2276	85.3
200	1 st (Day 1)	743	228	1608	85.0
	2 nd (Day 1)	1012	281	2443	89.2
	9 th (Day 5)	1361	383	3575	93.4
300	1 st (Day 1)	987	307	2124	90.7
	2 nd (Day 1)	1347	378	3202	93.6
	9 th (Day 5)	1800	498	4670	95.7
400	1 st (Day 1)	1209	378	2565	94.0
	2 nd (Day 1)	1657	468	3879	95.3
	9 th (Day 5)	2197	605	5679	97.4
500	1 st (Day 1)	1417	449	2979	95.5
	2 nd (Day 1)	1952	552	4516	96.5
	9 th (Day 5)	2563	704	6640	97.8

(Source: Applicant's Population PK Report, Table 9)

As shown in **Figure 2**, the predicted PK profile of NIR/r 300/100 mg q12h) based on the applicant's population PK model generally agreed with the observed data from the ongoing Phase 2/3 EPIC-HR study (data cutoff date 28 Oct 2021).

Figure 2. Median and 90% Prediction Intervals for NIR Concentration Overlaid with Observed Data from EPIC-HR Study (C4671005)



Symbols represent individual observations; Orange diamonds represent median of Day 5 observations binned by intervals (0,1,2,3,4,6,9,11,14 hours post-dose); Dashed horizontal line represents the target exposure EC90. Excluded observations with time after dose >14 hours. EC90 = concentration required for 90% of maximum effect. Samples below limit of quantification are shown below the LLOQ of 10 ng/mL.

(Source: Applicant's Population PK Evaluation of Interim data from Study C4671005, Figure 4)

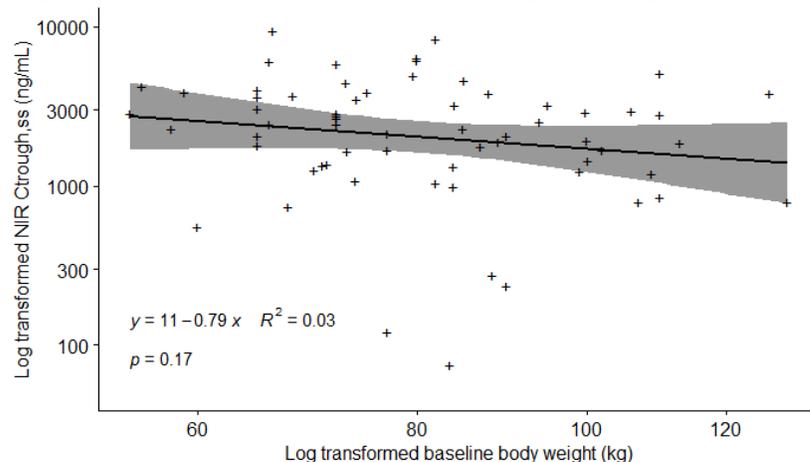
Reviewer's Comments: The preliminary population PK model appears reasonably unbiased based on the overlay with the observed PK data in adult patients with COVID-19. The selection of NIR/r 300/100 mg BID dose based on the predicted C12h above EC90 was further supported by efficacy data (Section VIII Human Clinical Efficacy).

Dose of NIR/r 300/100 mg BID in pediatrics 12 years and older

The applicant used the population PK model (standard weight allometry) to predict pediatric exposures. Due to the less than dose proportional increase in NIR exposures, half of the adult dose (taking one 150 mg NIR tablet instead of two with one 100 mg ritonavir tablet) is expected to have less than 50% reduction in exposure, and was evaluated in parallel with the adult dose. A dose of NIR/r 150/100 mg BID in adolescents provides lower AUC, Cmax, and Cmin, by 14%, 6%, and 22%, respectively, as compared to adults. In comparison, a dose of NIR/r 300/100 mg BID in adolescents provides higher NIR AUC, Cmax and Cmin by 32%, 37% and 25%, respectively, as compared to adults receiving the same dose. Overall, both doses are considered comparable to adults. To maintain Cmin comparable to adults in consideration of efficacy, the adult dose was proposed for pediatrics 12 years and older.

Considering that the standard weight allometry was applied, which was not evaluated in the current population PK modeling (the estimated effect of weight has a large uncertainty given the narrow weight range explored), the impact was graphically explored by the reviewer using the available sparse PK data from the Phase 2/3 EPIC-HR study submitted at the time of the review. As steady state Ctrough (C12h) is highly correlated with CL, the $C_{trough} \propto 1/CL = 1/(\text{weight}/70 \text{ kg})^{\theta}$ can be log transformed and expressed as $\text{Log}(C_{trough}) \propto -\theta \cdot \text{Log}(\text{weight}/70 \text{ kg})$. Therefore, the slope of the linear regression between $\text{Log}(C_{trough})$ and $\text{Log}(\text{weight})$ corresponds to the negative theta which is the exponent of the weight allometry if it is estimated. As shown in the **Figure 3**, theta is approximately 0.79 (slope of -0.79) which is very close to 0.75, indicating the standard weight allometry is appropriate to account for the impact of weight on clearance.

Figure 3. Relationship Between Log(Ctrough) and Log(weight)

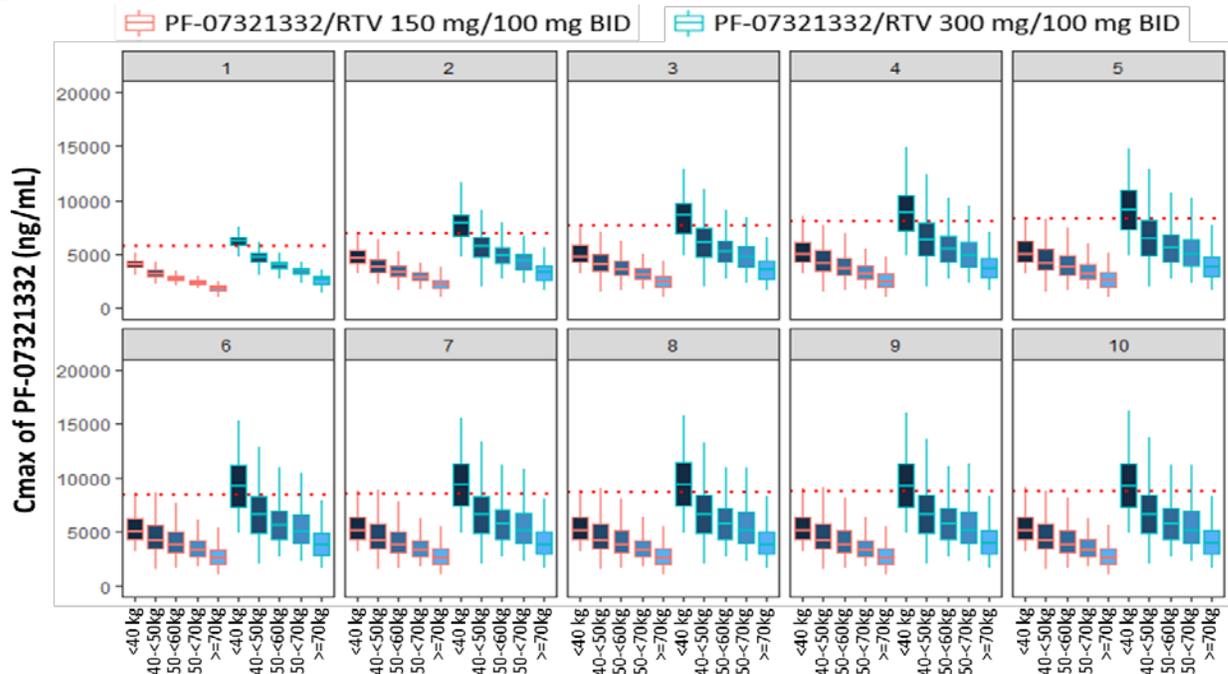


Ctrough: PK observations >100 hours since 1st dose, and between 10 and 14 hours (range for C12h) after the last dose. Linear regression line and confidence interval are represented by the solid line and grey band. The linear reregression formula, R², and p-value are indicated on the plot.

(Source: Reviewer's independent analysis)

In evaluation of the adult dose in pediatrics with a lower weight, especially under 40 kg which is not covered by the adult body weight range (42-158 kg) in the Phase 2/3 Study C4671005, the reviewer simulated C_{max} using the population PK model and NHANES data (2017-2020 pre-pandemic) for pediatrics 12 years and older by weight band as well as adults. The 95th percentile of predicted C_{max} in adults was used as the safety margin to check the appropriateness of the dose. For pediatrics under 40 kg receiving NIR/r 300/100 mg BID, about 50% of the subjects are expected to achieve C_{max} over the safety margin (**Figure 4**), which is not acceptable for the lack of safety data.

Figure 4. Predicted C_{max} Grouped by Weight Band for Pediatrics for 5 Days of BID Doses



Red dashed lines indicate 95th percentile of the predicted C_{max} of adults for the dose number indicated in the panel label.

(Source: Reviewer's independent analysis)

Reviewer's Comments:

Gender or age effect has not been assessed in adults and no pediatric data are available for evaluation. Generally, it is reasonable to apply weight allometry to predict exposure in adolescents and assess the exposure comparability to adults [Momper et al. JAMA Pediatr. 2013; Leong et al. CPT, 2021]. Based on the applicant's assessment, the adult dose was proposed for pediatrics 12 years and older weighing at least 40 kg. The reviewer's independent assessment further suggests that the adult dose might not be appropriate given the expected higher C_{max} in the low body weight pediatrics (<40 kg). NIR/r 150/100 mg BID could potentially provide comparable exposure for pediatrics 12 years and older weighing less than 40 kg to that in adults. However, the PK/efficacy/safety for adults <40 kg has not been established.

Reviewer’s independent analysis: Potential dose of NIR/r which could be evaluated in future clinical trials in patients with severe renal impairment

NIR/r in patients with severe renal impairment is not recommended and needs to be further assessed in clinical studies (See contents for the safety and condition of authorization in Section IX Human Clinical Safety Study C4671011). To streamline the development process, the reviewer applied the population PK model and the relative change in CL resulted from renal impairment (Study C4671011) to propose a dose that can be further tested in clinical studies (**Table 5**).

Table 5. Relative CL in Renal Impairment to Normal Renal Function

	Normal (eGFR ≥90 mL/min)	Mild (eGFR 60-<90 mL/min)	Moderate (eGFR 30-<60 mL/min)	Severe (eGFR <30 mL/min and not requiring dialysis)
CL/F	6.913	5.581	3.689	2.27
% relative to normal	100%	80.7%	53.4%	32.8%
Proposed dose (NIR/r)	300/100 mg BID	300/100 mg BID	150/100 mg BID	300/100 mg on Day 1* 150/100 mg QD on Day2-5*

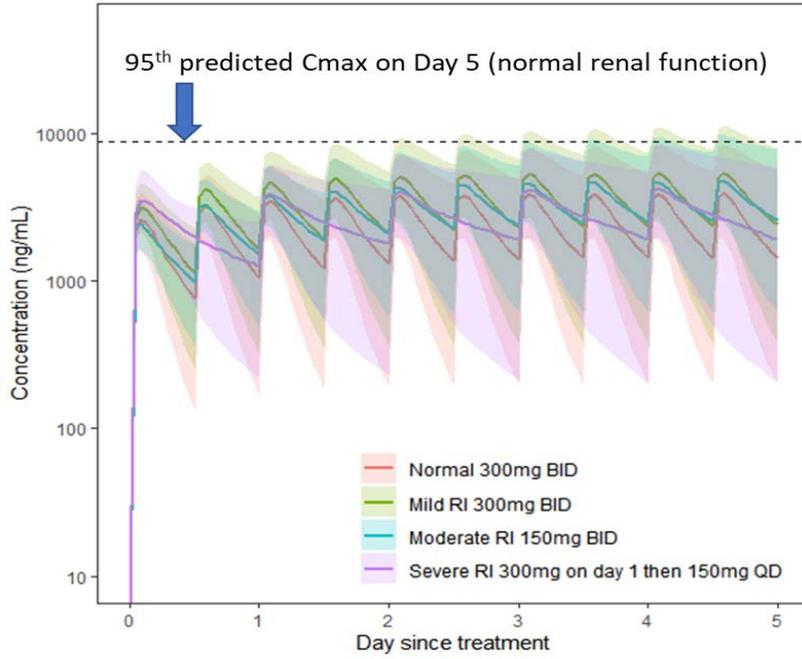
*Dose proposed for future evaluation only.

(Source: EUA request Table 20 and reviewer’s independent analysis)

Simulation was carried out for all grades of renal impairment, with mild and moderate as a proof-of-concept for dose evaluation based on NHANES adult data grouped by renal function category defined by eGFR (Cockcroft-Gault formula). The median of the simulated AUCs for mild and moderate renal impairment receiving NIR/r 100/100 mg, and the relative ratio to that of normal renal function, align with the exposure reported in Study C4671011. At the recommended doses (**Table 5**) for subjects with mild and moderate renal impairment, as shown in **Figure 5**, the PK profiles are slightly higher (7% and 12% higher in C_{max} and AUC_{0-24h} on day 5, but not expect to be clinically relevant) than that of normal renal function. For severe renal impairment, the potential dose (NIR/r 300/100mg on Day 1 followed by 150/100 mg QD on Day 2-5 of treatment) is predicted to achieve the highest C_{max} on Day 1, which is covered by the C_{max} of subjects with normal renal function from Day 2-5. The dose of 150/100 mg QD on Day 2-5 in the severe patients is expected to provide similar C_{max}, higher C_{trough}, and comparable C_{avg} to those for subjects with normal renal function. Therefore, this potential dose is anticipated to provide comparable efficacy for subjects with severe renal impairment. However, given the current safety concerns for subjects with severe renal impairment at the 100/100 mg single dose (Section IX Human Clinical Safety Study C4671011), this dose needs to be further evaluated in future clinical trials.

Overall, pending the safety data of this patient cohort from additional clinical studies, the proposed dose at the current stage only reflects our assessment from PK matching perspective with adults of normal renal function, and no recommendation of usage in patients with severe renal impairment should be made at this stage.

Figure 5. Predicted PK profile Grouped by Renal Function Category at the Proposed Dose



The color line and ribbon represent the median and 90% prediction interval respectively for each renal function category receiving the proposed dose

(Source: Reviewer's independent analysis)

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)

These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use

Original EUA Authorized Date: 12/2021

----- EUA FOR PAXLOVID -----

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro; also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in 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.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use as treatment of COVID-19. (1)

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----- DOSAGE AND ADMINISTRATION -----

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)

Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1)

- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min):** 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.2)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.2, 8.6)
- PAXLOVID is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). (2.3, 8.7)

----- DOSAGE FORMS AND STRENGTHS -----

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

----- CONTRAINDICATIONS -----

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with 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. (4)

----- WARNINGS AND PRECAUTIONS -----

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.2)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.3)

----- ADVERSE REACTIONS -----

Adverse events (incidence ≥1% and ≥5 subject difference) were dysgeusia, diarrhea, hypertension, and myalgia. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 [online](#), (2) by [downloading](#) this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

----- DRUG INTERACTIONS -----

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (2.4, 4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in 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 risk¹ for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 [see *Dosage and Administration (2.1)*].²
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

¹ For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

² Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
 - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
 - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no approved alternatives to PAXLOVID 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.

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

The dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next

dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food [see *Clinical Pharmacology* (12.3)]. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Important Dosing Information in Patients with Renal Impairment

No dosage adjustment is needed 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 dosage of PAXLOVID is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions [see *Patient Counseling Information* (17)].

PAXLOVID is not recommended in patients with severe renal impairment (eGFR < 30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

2.3 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment [see *Use in Specific Populations* (8.7)].

2.4 Important Drug Interactions with PAXLOVID

No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat.

Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

Refer to other sections of the Fact Sheet for important drug interactions with PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy [see *Contraindications* (4), *Warnings and Precautions* (5.1), and *Drug Interactions* (7)].

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side. Each tablet contains 150 mg of nirmatrelvir.
- Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions [see *Drug Interactions (7.3)*]:

- Alpha₁-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is contraindicated with drugs that are 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. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer [see *Drug Interactions (7.3)*]:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for PAXLOVID. Serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID use.

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.

- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See Table 1 for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications [see *Contraindications (4) and Drug Interactions (7)*].

5.2 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.3 Risk of HIV-1 Resistance Development

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 [see *Dosage and Administration (2.4), Contraindications (4), and Drug Interactions (7)*].

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of PAXLOVID that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with PAXLOVID may become apparent with more widespread use.

The safety of PAXLOVID is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection [see *Clinical Studies (14.1)*]. A total of 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either PAXLOVID (n=1,109) or placebo (n=1,115). Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the PAXLOVID group ($\geq 1\%$) that occurred at a greater frequency (≥ 5 subject difference) than in the placebo group were dysgeusia (6% and $<1\%$, respectively), diarrhea (3% and 2%), hypertension (1% and $<1\%$), and myalgia (1% and $<1\%$).

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event, using FDA Form 3500 (for information on how to access

this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: <https://www.fda.gov/medwatch/report.htm>
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
 - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
 - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with PAXLOVID.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. 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 [see *Contraindications (4) and Table 1*]. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides listing of clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult appropriate references for comprehensive information [see *Contraindications (4)*].

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension [see <i>Contraindications (4)</i>].
Analgesics	pethidine, piroxicam, propoxyphene	↑ pethidine ↑ piroxicam ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities [see <i>Contraindications (4)</i>].
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions [see <i>Contraindications (4)</i>].
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias [see <i>Contraindications (4)</i>].
Antiarrhythmics	bepidil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance [see <i>Contraindications (4)</i>].

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepine ^a , phenobarbital, phenytoin	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance [see <i>Contraindications (4)</i>].
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazodone product label for further information.
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate itraconazole ^a	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment [see <i>Contraindications (4)</i>].
Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ protease Inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors [see <i>Dosage and Administration (2.4)</i>].
Anti-HIV	didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered [see <i>Contraindications (4)</i>].
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias [see <i>Contraindications (4)</i>].

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system [see <i>Contraindications (4)</i>].

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir ombitasvir/paritaprevir /ritonavir and dasabuvir sofosbuvir/velpatasvir/ voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use [see <i>Dosage and Administration (2.4)</i>].
Herbal products	St. John's Wort (<i>hypericum perforatum</i>)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance [see <i>Contraindications (4)</i>].
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis [see <i>Contraindications (4)</i>]. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	fentanyl methadone	↑ fentanyl ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PAXLOVID. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope [see <i>Contraindications (4)</i>].
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression [see <i>Contraindications (4)</i>].

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage (*see Data*). There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (*see Clinical Considerations*).

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID (*see Data*).

In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of PAXLOVID (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S.

general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir

Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,400 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% confidence interval [CI]: 1.9%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.6%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir

Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and 6 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC₂₄) in rats was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC₂₄) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed at up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC₂₄) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 is ongoing and only interim data through postnatal day (PND) 56 are currently available. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease (8% in males and females) in the body weight of offspring was observed at PND 17. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC₂₄) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure

(AUC₂₄) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

Ritonavir

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor. In a pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir (*see Data*). Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data

In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC₂₄) approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC₂₄) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception [*see Drug Interactions (7.3)*].

8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy [see *Adverse Reactions (6.1)* and *Clinical Studies (14.1)*]. Of the total number of subjects in EPIC-HR randomized to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

8.6 Renal Impairment

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment [see *Clinical Pharmacology (12.3)*].

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), reduce the dose of PAXLOVID to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions [see *Patient Counseling Information (17)*].

PAXLOVID is not recommended in patients with severe renal impairment (eGFR < 30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

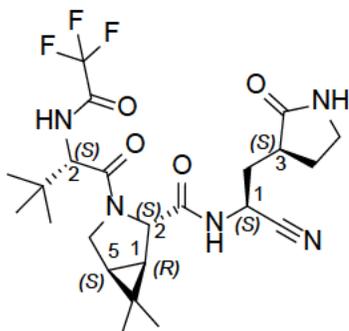
Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

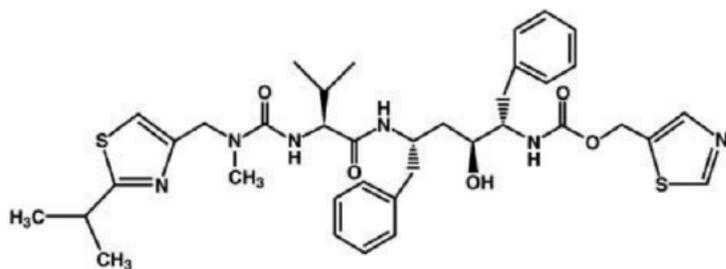
The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide. It has a molecular formula of C₂₃H₃₂F₃N₅O₄ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5*S*-(5*R*^{*},8*R*^{*},10*R*^{*},11*R*^{*})]. Its molecular formula is C₃₇H₄₈N₆O₅S₂, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 Mpro active site by X-ray crystallography.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy subjects.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.

Upon oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure appears to be less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses. Twice daily dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00 ^a	3.98 ^a
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14 ^c
V_z/F (L), mean	104.7 ^b	112.4 ^b
Elimination		
Major route of elimination	Renal elimination ^d	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05 ^a	6.15 ^a
Oral clearance (CL/F), mean	8.99 ^b	13.92 ^b
Metabolism		
Metabolic pathways	Minimal ^d	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6% ^e	86.4% ^f
% drug-related material in urine	35.3% ^e	11.3% ^f

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

- 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.
- 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
- Red blood cell to plasma ratio.
- Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
- Determined by ¹⁹F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
- Determined by ¹⁴C analysis following 600 mg ¹⁴C-ritonavir oral solution.

Single dose pharmacokinetic data of PAXLOVID in healthy subjects is depicted below (Table 3).

Table 3: Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects

PK Parameter (units)	Nirmatrelvir (N=12)
C _{max} (µg/mL)	2.21 (33)
AUC _{inf} (µg*hr/mL)	23.01 (23)
T _{max} (hr)	3.00 (1.02-6.00)
T _{1/2} (hr)	6.05 ± 1.79

Represents data from 2 x 150 mg tablets of nirmatrelvir. Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for T_{1/2}.

Effect of Food on Oral Absorption of Nirmatrelvir

Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Specific Populations

The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.

Pediatric Patients

The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been evaluated.

Using a population PK model, the dosing regimen is expected to result in comparable steady-state plasma exposure of nirmatrelvir in patients 12 years of age and older and weighing at least 40 kg to those observed in adults after adjusting for body weight.

Racial or Ethnic Groups

Systemic exposure in Japanese subjects was numerically lower but not clinically meaningfully different than those in Western subjects.

Patients with Renal Impairment

An open-label study compared nirmatrelvir/ritonavir pharmacokinetics in healthy adult subjects and subjects with mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe (eGFR <30 mL/min) renal impairment following administration of a single oral dose of nirmatrelvir 100 mg enhanced with ritonavir 100 mg administered at -12, 0, 12, and 24 hours. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87%

higher, and in patients with severe renal impairment was 48% and 204% higher, respectively (Table 4).

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C _{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC _{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T _{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
T _{1/2} (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for t_{1/2}.

Patients with Hepatic Impairment

A single oral dose of 100 mg nirmatrelvir enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar exposures compared to subjects with normal hepatic function (Table 5).

Table 5: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Hepatic Function (n=8)	Moderate Hepatic Impairment (n=8)
C _{max} (µg/mL)	1.89 (20)	1.92 (48)
AUC _{inf} (µg*hr/mL)	15.24 (36)	15.06 (43)
T _{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)
T _{1/2} (hr)	7.21 ± 2.10	5.45 ± 1.57

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for t_{1/2}.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Drug Interaction Studies Conducted with Nirmatrelvir

In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and 3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations. Nirmatrelvir has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp).

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

Drug Interaction Studies Conducted with Ritonavir

In vitro studies indicate that ritonavir is mainly a substrate of CYP3A. Ritonavir also appears to be a substrate of CYP2D6 which contributes to the formation of isopropylthiazole oxidation metabolite M-2.

Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

The effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarized in Table 6 (effect of other drugs on nirmatrelvir).

Table 6: Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-administered Drugs

Co-administered Drug	Dose (Schedule)		N	Ratio (in combination with Co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/Ritonavir		C_{max}	AUC ^a
Carbamazepine ^b	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max} =maximum plasma concentrations.

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).

12.4 Microbiology

Antiviral Activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC₅₀ and EC₉₀ values of 62 nM and 181 nM, respectively, after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC₅₀ values ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

No data are available regarding the activity of nirmatrelvir against the SARS-CoV-2 Omicron (B.1.1.529) variant in cell culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce nirmatrelvir activity (K_i fold change <1) compared to the USA-WA1/2020 enzyme.

Antiviral Activity Against SARS-CoV-2 in Animal Models

Nirmatrelvir showed antiviral activity in BALB/c and 129 mice infected with mouse-adapted SARS-CoV-2. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post-inoculation resulted in reduction of lung viral titers and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

Antiviral Resistance

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARS-CoV-2 Mpro polymorphisms on the activity of nirmatrelvir in a biochemical assay using recombinant Mpro enzyme. The clinical significance of these polymorphisms is unknown, and it is also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (≥ 3 -fold higher K_i values): G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). G15S is present in the Lambda variant, which did not have reduced susceptibility to nirmatrelvir (relative to USA-WA1/2020) in cell culture.

In addition, three SARS-CoV-2 Mpro amino acid positions where polymorphisms have not been naturally observed were evaluated by substituting alanine at these positions and assessing their impact on activity in biochemical assays. These Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher K_i values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of substitutions at these Mpro positions is unknown.

Cell culture resistance selection studies with nirmatrelvir using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The clinical relevance of these changes is not known. The presence of the substitutions P55L and S144A was associated with reduced nirmatrelvir susceptibility (~ 4 - to 5-fold higher EC_{50} values). These positions correspond to E55 and S144 in SARS-CoV-2 Mpro, respectively. E55L alone did not affect nirmatrelvir activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A reduced nirmatrelvir activity by 91.9-fold (based on K_i value).

Limited SARS-CoV-2 sequencing data are available to characterize nirmatrelvir resistance in clinical trials. The SARS-CoV-2 Mpro substitutions A260V ($n=3$) or A260T ($n=1$) emerged in 4% (4/97) of nirmatrelvir/ritonavir treated subjects in clinical trial EPIC-HR with available sequence analysis data. A260T and A260V substitutions are infrequent natural polymorphisms in publicly available SARS-CoV-2 sequences (as of Dec 5, 2021). In a biochemical assay, the A260V Mpro substitution did not reduce nirmatrelvir activity (K_i fold-change < 1).

Cross-resistance is not expected between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for

males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC₂₄) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 2 times higher (in males) than the exposure in humans at the authorized human dose of PAXLOVID. There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 4 times higher (in females) than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 36% that of the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 2 (male) and 4 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

13.2 Animal Toxicology and/or Pharmacology

Studies with nirmatrelvir included repeat dose toxicity studies in rats (14 days) and monkeys (15 days). Repeated daily oral dosing in rats at up to 1,000 mg/kg/day resulted in non-adverse hematological, liver, and thyroid effects. All of the hematology and coagulation findings (i.e., increases in PT and APTT) had no clinical or microscopic correlates and all findings completely recovered at the end of the 2-week recovery period. 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 occurred in the absence of correlating alterations in clinical pathology parameters, and all of these findings fully recovered. No adverse effects were observed at doses up to 1,000 mg/kg/day, resulting in systemic exposure approximately 4 times higher than exposures at the authorized human dose of PAXLOVID. Nirmatrelvir-related findings following repeat oral dosing in monkeys for 15 days were limited to emesis and increase in fibrinogen. Increased fibrinogen may be attributed to an inflammatory state but lacked a microscopic correlate. At the high dose of 600 mg/kg/day, the systemic exposure in monkeys was about 18 times higher than exposures at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progressing to Severe COVID-19 Illness

The data supporting this EUA are based on the analysis of EPIC-HR (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of

age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set (all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,246 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 46 years; 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from initiation of study treatment; 47% of subjects were serological negative at baseline; the mean (SD) baseline viral load was 4.63 log₁₀ copies/mL (2.87); 26% of subjects had a baseline viral load of >10⁷ (units); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

Table 7 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%).

Table 7: Efficacy Results in Non-Hospitalized Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did Not Receive COVID-19 Monoclonal Antibody Treatment at Baseline (mITT1 Analysis Set)

	PAXLOVID (N=1,039)	Placebo (N=1,046)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo ^a [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

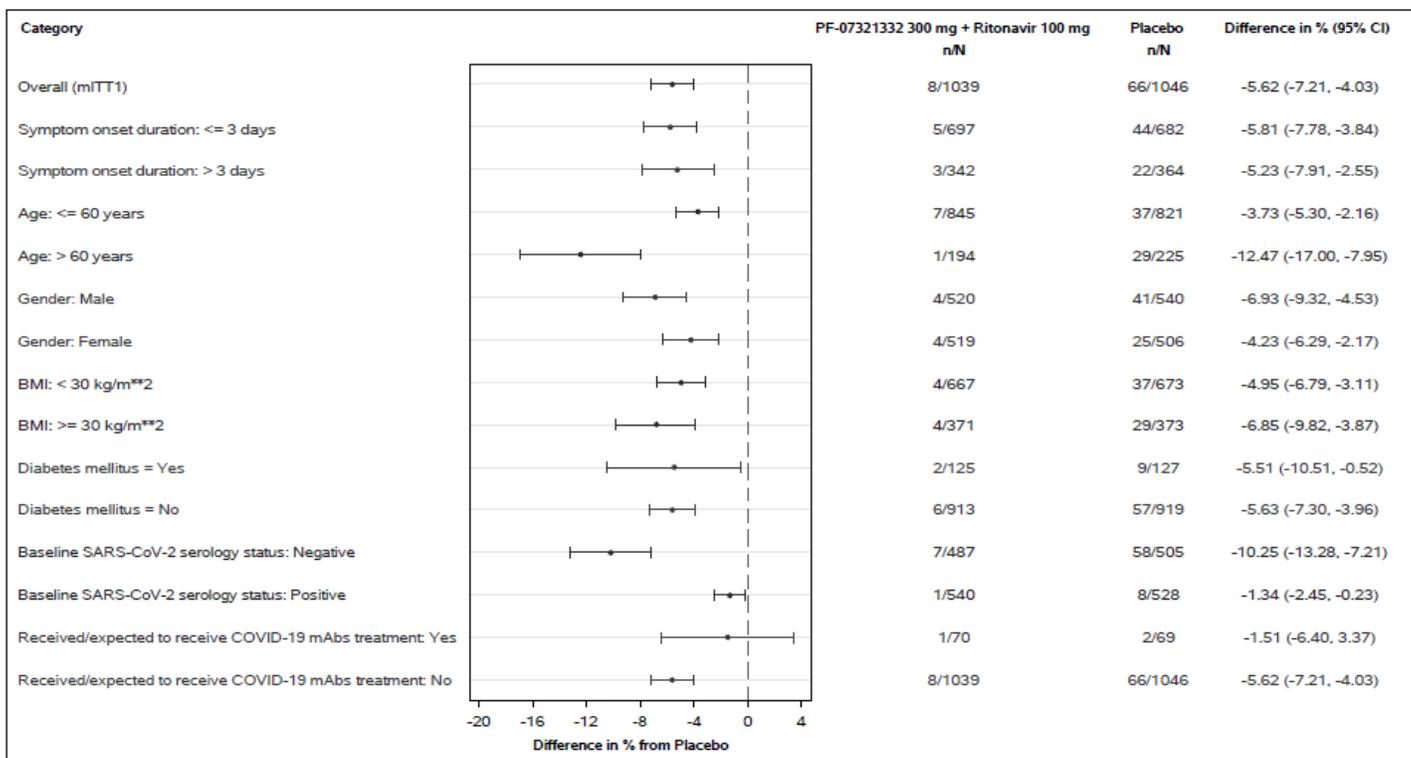
The determination of primary efficacy was based on a planned interim analysis of 780 subjects in mITT population. The estimated risk reduction was -6.3% with a 95% CI of (-9.0%, -3.6%) and 2-sided p-value <0.0001.

a. The estimated cumulative proportion of participants hospitalized 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.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the PAXLOVID group, and 44/682 (6.45%) in the placebo group. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.

Similar trends have been observed across subgroups of subjects (see Figure 1). These subgroup analyses are considered exploratory.

Figure 1: Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 (Protocol C4671005)



N=number of participants in the category of the analysis set.

All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.

Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.

The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Relative to placebo, PAXLOVID treatment was associated with an approximately 0.9 log₁₀ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Each carton contains 30 tablets divided in 5 daily-dose blister cards (NDC number: 0069-1085-30).

Each daily blister card (NDC number: 0069-1085-06) contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the “FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS” and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Use in Patients with Renal Impairment

No dose adjustment is needed in patients with mild renal impairment.

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days. Instruct patients that the pharmacist will alter their daily blister cards to ensure they receive the correct dose.

Pharmacist should refer to the provided instructions entitled “IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT” for dispensing of PAXLOVID to patients with moderate renal impairment [see *Dosage and Administration (2.2)*].

Appropriate dosage for patients with severe renal impairment has not been determined [see *Dosage and Administration (2.2)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

Drug Interactions

Inform patients that PAXLOVID may interact with some drugs and is contraindicated for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products [see *Dosage and Administration (2.4)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Drug Interactions (7)*].

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take

the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose [see *Dosage and Administration (2.1)*].

18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
<p data-bbox="240 411 620 445">www.COVID19oralRx.com</p> 	<p data-bbox="971 499 1240 583">1-877-219-7225 (1-877-C19-PACK)</p>

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.



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FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF PAXLOVID FOR CORONAVIRUS DISEASE 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with PAXLOVID for the treatment of mild-to-moderate coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus. This Fact Sheet contains information to help you understand the risks and benefits of taking the PAXLOVID you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make PAXLOVID available during the COVID-19 pandemic (for more details about an EUA please see “**What is an Emergency Use Authorization?**” at the end of this document). PAXLOVID is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about PAXLOVID. Talk to your healthcare provider about your options or if you have any questions. It is your choice to take PAXLOVID.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is PAXLOVID?

PAXLOVID is an investigational medicine used to treat mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (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. PAXLOVID is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PAXLOVID to treat people with mild-to-moderate COVID-19.

The FDA has authorized the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with a positive test for the virus that causes COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

What should I tell my healthcare provider before I take PAXLOVID?

Tell your healthcare provider if you:

- Have any allergies
- Have liver or kidney disease
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illnesses

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with PAXLOVID and may cause serious side effects. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with PAXLOVID. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take PAXLOVID with other medicines.

Tell your healthcare provider if you are taking combined hormonal contraceptive.

PAXLOVID may affect how your birth control pills work. Females who are able to become pregnant should use another effective alternative form of contraception or an additional barrier method of contraception. Talk to your healthcare provider if you have any questions about contraceptive methods that might be right for you.

How do I take PAXLOVID?

- PAXLOVID consists of 2 medicines: nirmatrelvir and ritonavir.
 - Take 2 pink tablets of nirmatrelvir with 1 white tablet of ritonavir by mouth 2 times each day (in the morning and in the evening) for 5 days. **For each dose, take all 3 tablets at the same time.**
 - **If you have kidney disease, talk to your healthcare provider. You may need a different dose.**
- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- Take PAXLOVID with or without food.
- Do not stop taking PAXLOVID without talking to your healthcare provider, even if you feel better.
- If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.
- If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you are taking a ritonavir- or cobicistat-containing medicine to treat hepatitis C or Human Immunodeficiency Virus (HIV), you should continue to take your medicine as prescribed by your healthcare provider.

Talk to your healthcare provider if you do not feel better or if you feel worse after 5 days.

Who should generally not take PAXLOVID?

Do not take PAXLOVID if:

- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID.
- You are taking any of the following medicines:
 - Alfuzosin
 - Pethidine, piroxicam, propoxyphene
 - Ranolazine
 - Amiodarone, dronedarone, flecainide, propafenone, quinidine
 - Colchicine
 - Lurasidone, pimozone, clozapine
 - Dihydroergotamine, ergotamine, methylergonovine
 - Lovastatin, simvastatin
 - Sildenafil (Revatio®) for pulmonary arterial hypertension (PAH)
 - Triazolam, oral midazolam
 - Apalutamide
 - Carbamazepine, phenobarbital, phenytoin
 - Rifampin
 - St. John's Wort (*hypericum perforatum*)

Taking PAXLOVID with these medicines may cause serious or life-threatening side effects or affect how PAXLOVID works.

These are not the only medicines that may cause serious side effects if taken with PAXLOVID. PAXLOVID may increase or decrease the levels of multiple other medicines. It is very important to tell your healthcare provider about all of the medicines you are taking because additional laboratory tests or changes in the dose of your other medicines may be necessary while you are taking PAXLOVID. Your healthcare provider may also tell you about specific symptoms to watch out for that may indicate that you need to stop or decrease the dose of some of your other medicines.

What are the important possible side effects of PAXLOVID?

Possible side effects of PAXLOVID are:

- **Liver Problems.** Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain.
- **Resistance to HIV Medicines.** If you have untreated HIV infection, PAXLOVID may lead to some HIV medicines not working as well in the future.

- **Other possible side effects include:**

- altered sense of taste
- diarrhea
- high blood pressure
- muscle aches

These are not all the possible side effects of PAXLOVID. Not many people have taken PAXLOVID. Serious and unexpected side effects may happen. PAXLOVID is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?

Like PAXLOVID, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with PAXLOVID. Should you decide not to receive it or for your child not to receive it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?

There is no experience treating pregnant women or breastfeeding mothers with PAXLOVID. For a mother and unborn baby, the benefit of taking PAXLOVID may be greater than the risk from the treatment. If you are pregnant, discuss your options and specific situation with your healthcare provider.

It is recommended that you use effective barrier contraception or do not have sexual activity while taking PAXLOVID.

If you are breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with PAXLOVID?

Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 or you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

How should I store PAXLOVID?

Store PAXLOVID tablets at room temperature, between 68°F to 77°F (20°C to 25°C).

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit <https://www.cdc.gov/COVID19>.
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?

The United States FDA has made PAXLOVID available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (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, has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for PAXLOVID is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless terminated or revoked (after which the products may no longer be used under the EUA).

Additional Information

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
<p data-bbox="305 359 683 394">www.COVID19oralRx.com</p> 	<p data-bbox="1036 443 1305 533">1-877-219-7225 (1-877-C19-PACK)</p>

You can also go to www.pfizermedinfo.com or call 1-800-438-1985 for more information.



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December 22, 2021

IMPORTANT PRESCRIBING INFORMATION

Subject: PAXLOVID Emergency Use Authorization (EUA) dosing and dispensing in moderate renal impairment, and risk of serious adverse reactions due to drug interactions

Dear Healthcare Provider,

The purpose of this letter is to make you aware of the EUA dosing and dispensing requirements for patients with moderate renal impairment, and the potential for drug-drug interactions associated with PAXLOVID (nirmatrelvir tablets; ritonavir tablets). PAXLOVID contains two different drugs that are co-packaged in a daily blister card for oral use.

The dosage for PAXLOVID is as follows:

eGFR*	PAXLOVID Dose
Greater than 60 mL/min (<i>normal renal function or mild renal impairment</i>)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to <60 mL/min (<i>moderate renal impairment</i>)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30 mL/min (<i>severe renal impairment</i>)	PAXLOVID is not recommended (the appropriate dose has not been determined).

*eGFR=estimated glomerular filtration rate based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula

Each daily blister card contains a morning and evening dose, with each dose consisting of 300 mg nirmatrelvir (two oval, pink 150 mg tablets) and 100 mg ritonavir (one ovaloid, white 100 mg tablet) as shown in Figure A below, which is incongruent with the moderate renal impairment dose.

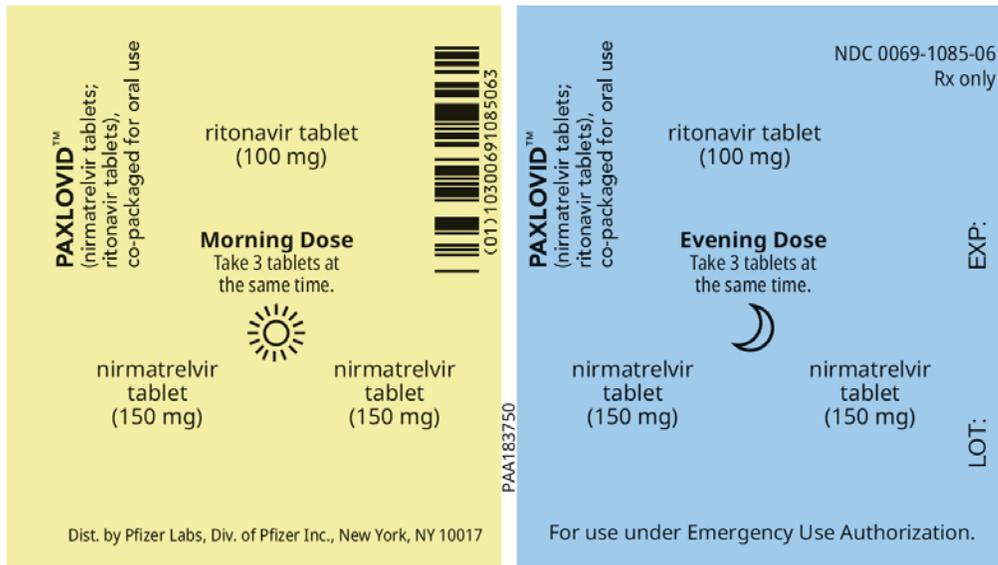


Figure A: Blister card containing morning and evening dose for normal renal function or mild renal impairment

Each daily blister card contains more nirmatrelvir tablets than are needed for dosing in patients with moderate renal impairment. **It is critical that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:**

- **PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or**
- **PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment**

Dispensing information in patients with moderate renal impairment:

Each shipment of PAXLOVID will be accompanied with **instructions, for pharmacists to remove the unneeded, additional nirmatrelvir tablets, and with stickers to affix to each daily blister card as well as the carton** when dispensing PAXLOVID to patients with moderate renal impairment (see below for image of dispensing instructions).

Pharmacists should ensure that they refer to the instructions entitled “IMPORTANT PAXLOVID™ DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT” regarding specific instructions on tablet removal and proper sticker placement. In addition, **pharmacists should counsel patients** about renal dosing instructions and notify them that their blister cards have been altered at the pharmacy.

IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH **MODERATE RENAL IMPAIRMENT**

To dispense PAXLOVID dose (150 mg nirmatrelvir with 100 mg ritonavir) for moderate renal impairment, pharmacist should:

STEP ONE: Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of the blister card (see figure 1 below). The nirmatrelvir tablets that are removed should be the ones closest to the middle of the blister pack.

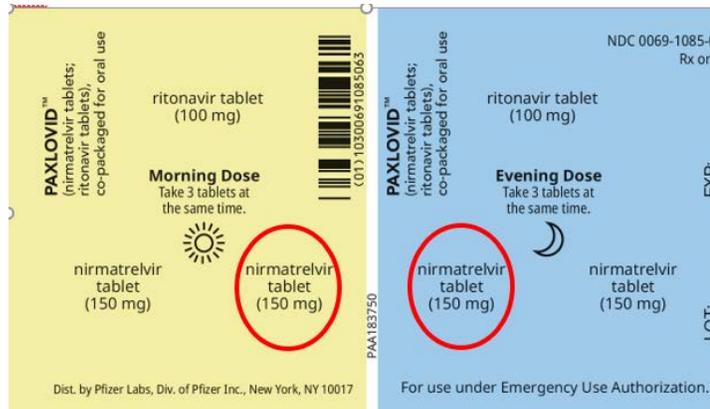


Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

STEP TWO: Affix the blister card with one sticker from the provided tear pad to carefully cover the empty blister cavities as shown in figure 2 below. The exact placement of this sticker is important to cover the empty blister cavities from the tablets. Ensure the sticker also covers the pre-printed dosing instruction that is on the blister card.

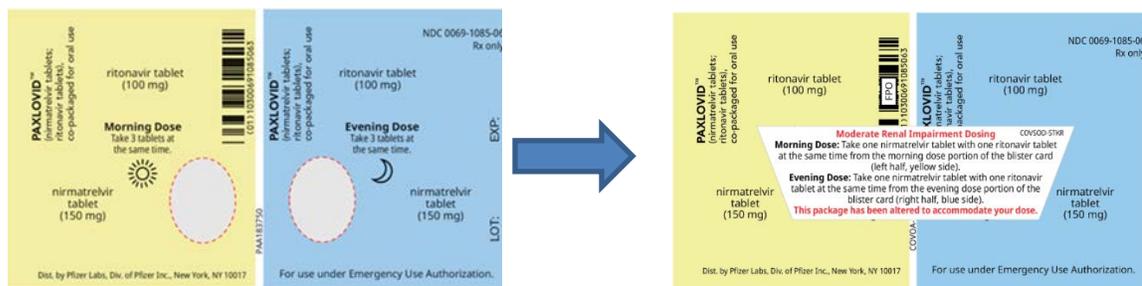


Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

STEP THREE: Repeat steps one and two for every blister card in the carton (each carton contains five blister cards for a full 5-day dosing regimen).

STEP FOUR: Affix one sticker from the provided tear pad to carefully cover over the pre-printed dosing regimen on the carton as shown in figure 3 below:



Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Patients with moderate renal impairment should be instructed to take only one 150-mg nirmatrelvir tablet with one 100-mg ritonavir tablet together twice daily for 5 days. **Patients with moderate renal impairment should be notified that their blister cards have been altered by their pharmacist to remove unneeded tablets.**

Risk of Serious Adverse Reactions Due to Drug Interactions:

Use of PAXLOVID, a CYP3A inhibitor, in patients receiving concomitant medications metabolized by CYP3A may increase the plasma concentrations of those concomitant medications.

Use of concomitant medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See the current EUA Fact Sheet for Healthcare Providers for clinically significant drug interactions, including **contraindicated** drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Prescribers and pharmacists should inform patients that PAXLOVID may interact with some drugs and is **contraindicated** for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription or non-prescription medication or herbal products.

Indication & Authorized Use:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in 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.

For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>.

Healthcare providers should consider the benefit-risk for an individual patient.

Limitations of Authorized Use:

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

Reporting Adverse Events and Medication Errors:

Under the EUA, all serious adverse events and all medication errors potentially related to PAXLOVID must be reported.

Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (<https://www.fda.gov/media/76299/download>) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form. Please provide a copy of all FDA MedWatch forms to Pfizer via fax (1-866-635-8337), telephone (1-800-438-1985) or website www.pfizersafetyreporting.com

The PAXLOVID EUA Fact Sheet for Healthcare Providers is available at www.COVID19oralRx.com or by scanning the QR Code below:



Sincerely,

A handwritten signature in black ink, appearing to read "Eddie G M Power". The signature is stylized with a large, looped initial 'E' and a long horizontal stroke at the end.

Eddie G M Power PhD MBA GFMD
Vice President, North America Medical Affairs

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/

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