THE ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

MARCH 16, 2023

PAXLOVID™

(NIRMATRELVIR [PF-07321332] TABLETS; RITONAVIR TABLETS)

NDA 217188

Advisory Committee Briefing Materials: Available for Public Release

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GLOSSARY

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
BID	twice daily
C4671002 / Study 1002 / EPIC-SR	evaluation of protease inhibition for COVID-19 in standard-risk patients
C4671005 / Study 1005 / EPIC-HR	evaluation of protease inhibition for COVID-19 in high-risk patients
C4671006 / Study 1026 / EPIC-PEP	evaluation of protease inhibition for COVID-19 in post-exposure prophylaxis
C4671026 / Study 1006 / EPIC-Peds	evaluation of protease inhibition for COVID-19 in pediatric patients at risk of severe disease
CDC	Centre for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DDI	drug-drug interaction
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GISAID	global initiative on sharing avian influenza data
LPLV	last patient last visit
mAb	monoclonal antibody
mITT	modified intent-to-treat
mITT1	modified intent-to-treat 1
mITT2	modified intent-to-treat 2
mITT3	modified intent-to-treat 3
M^{pro}	main protease
NDA	New Drug Application
PD	pharmacodynamics
PK	pharmacokinetic(s)
Pop PK	population pharmacokinetics
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TEAE	treatment-emergent adverse event
TEMs	treatment-emergent mutations
US	United States
VL	viral load (viral RNA level in nasopharyngeal [NP] swabs)
VLR	viral load rebound
VOC	variant(s) of concern
VOI	variant of interest
WT	wild-type

1. EXECUTIVE SUMMARY

This briefing document supports the use of PAXLOVID™ (nirmatrelvir [PF-07321332] tablets; ritonavir tablets) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death (please refer to Table 1 for CDC guidance in determining underlying medical conditions associated with higher risk for severe COVID-19).

The antiviral testing strategy for nirmatrelvir has followed the FDA Guidance on Antiviral Drug Development[1] as well as the COVID-19 Guidance on Developing Drug and Biological Product.[2]

The briefing document is provided in advance of the Advisory Committee Meeting in support of the sponsor's NDA currently under review by the FDA.

1.1. COVID-19 Therapeutic Context

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2.[3] The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020.[4] On 04 February 2020, the Secretary of Health and Human Services (HHS) determined there was a public health emergency in the US.[5] On 11 March 2020, the WHO further characterized the disease outbreak as a pandemic.[6] In the US, the Secretary of HHS declared that circumstances existed justifying the authorization of emergency use of drugs and biologics during the COVID-19 pandemic effective 27 March 2020.[7] As of February 2023, worldwide there have been over 753 million confirmed cases, including 6.8 million deaths.[8]

Since the emergence of the virus, several VOC have emerged and rapidly spread with a global distribution.[9] Omicron, the current VOC, is somewhat distantly related to previous VOC and is of significant public health concern since it carries several mutations that were also found in other VOC and were associated with increased infectivity and enhanced capacity to evade the immune system.[10] In the US, as of late January 2023, the combined national proportion of lineages designated as Omicron continues to be 100%. There are currently six lineages designated as Omicron with estimates above 1%: In order of prevalence these are: XBB. 1.5, BQ. 1.1, BQ.1, XBB, CH. 1.1, and BN.1.[11] Additionally, the WHO's Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) has suggested that the XBB sublineage may also increase in prevalence over the coming months.[12]

Importantly, current uptake of mRNA bi-valent vaccines containing the ancestral and the BA 4/5 strains are relatively low,[13,14] compared to both the uptake of primary series and the first booster dose. This potentially leaves a greater proportion of individuals susceptible to new emerging BQ.1 and XBB sublineages.[11,14] Additionally, current mRNA vaccines have shown decreased levels of neutralizing antibodies against these latter sublineages which may potentially lead to erosion of vaccine effectiveness against severe disease over time.

Other COVID-19 treatment options are also being rendered ineffective by continual mutations in the spike protein of SARS-CoV-2. Emerging subvariants are likely to be

resistant to currently available anti-SARS-CoV-2 mAbs.[10] On 30 November 2022, the US FDA announced that the BQ.1 and BQ.1.1 had become the predominant virus strains causing infection in the US and as bebtelovimab is unlikely to neutralize these variants, withdrew the EUA for this product.[15] Similarly, the currently circulating Omicron variants are also likely to be resistant to tixagevimab plus cilgavimab (EVUSHELD). The FDA has announced that EVUSHELD is not currently authorized for use in the US as unlikely to neutralize these variants.[16] The anticipated loss of susceptibility is based on knowledge about amino acid mutations that confer resistance to anti-SARS-CoV-2 antibodies and on data from in vitro neutralization studies.[17] Due to this loss of effectiveness associated with the mAbs, the public must rely on other available treatment options including anti-viral agents against COVID-19.

Although the approved antiviral agent remdesivir is available for the treatment of COVID-19, it must be administered intravenously. An oral antiviral agent would offer an easy and convenient method of drug administration without requiring attendance at a healthcare setting. Targeting a highly conserved viral target essential for viral replication would provide an effective therapeutic agent against current and future coronavirus variants, especially in the context of rapidly mutating SARS-CoV-2 subvariants. Furthermore, a benefit-risk profile supportive of administration to patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease will significantly add to the treatment armamentarium for COVID-19. Such antivirals, when used early on in infection, could limit the impact of SARS-CoV-2 infections on the healthcare system, including overwhelmed hospital facilities and lack of ICU bed space.[18]

This briefing document describes the nonclinical studies, clinical development program, and benefit-risk of PAXLOVID, an oral potent and selective inhibitor of SARS-CoV-2 M^{pro}. PAXLOVID exhibits broad-spectrum activity across the Coronaviridae family of M^{pro}. PAXLOVID was granted an EUA on 22 December 2021 for use in individuals with mild-to-moderate COVID-19 who are at high risk of developing severe disease based on CDC criteria.[19] To date, there has been an estimated 8.6 million patient exposures of PAXLOVID in the US under the authorized EUA. The sponsor is now seeking full approval of PAXLOVID based on the data described herein.

1.2. Summary of Nonclinical Studies

Studies on the secondary pharmacology evaluated in vitro activity of nirmatrelvir against a wide panel of receptors, transporters, ion channels and enzyme assays. Results indicated no significant inhibition (>50%) of functional or enzymatic activity by nirmatrelvir (exposure margins ranged from ~50x-150x over the human unbound nirmatrelvir C_{max} of the clinical dose of PAXLOVID BID).

Safety pharmacology studies were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory), and only some minor, transient, and clinically monitorable effects (such as increased systolic, diastolic, and mean BP, HR decreases, and associated RR, PR, and QT interval increases) were seen.

The toxicity of nirmatrelvir has been evaluated in GLP repeat-dose toxicity studies up to 1 month in duration in 2 species. There were no adverse findings in any of the studies with margins >10x systemic exposures in human.

Nirmatrelvir had no adverse effects on male or female fertility in rats, fetal morphology or embryo-fetal viability in rats and rabbits, or pre- and postnatal development in rats when evaluated at doses up to 1000 mg/kg/day. The only adverse nirmatrelvir-related effect was lower fetal body weights at 1000 mg/kg/day in the presence of low magnitude effects on maternal body weight change and food consumption at this dose in the rabbit embryo fetal development study.

Nirmatrelvir was not mutagenic or clastogenic in in vitro genetic toxicity studies and was negative in the in vivo rat micronucleus assay incorporated into a GLP repeat-dose toxicity study. Nirmatrelvir does not present a photo toxicity risk based on ultraviolet-visible absorbance evaluation.

The nonclinical toxicity profile of ritonavir is well characterized. Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland, and kidney. Hepatic changes involved hepatocellular, biliary, and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all rodent studies conducted with ritonavir and may be secondary to phospholipidosis but have not been seen in dogs. Clinical trials revealed no evidence of ritonavir-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and were considered to be attributable to species-specific spontaneous disease. No clinically significant renal abnormalities were noted in clinical trials.

Ritonavir had no adverse effects on male or female fertility in rats or pre- and postnatal development in rats, and there was no evidence of teratogenicity in rats or rabbits. In the rat and rabbit embryo-fetal development studies, increased incidences of resorptions, ossification delays, developmental variations, decreased litter size, and/or decreased fetal weights were observed in the presence of maternal toxicity. Pregnant women (6100 live births) administered ritonavir during pregnancy (2800 exposed during first trimester) did not demonstrate an increased rate of birth defects compared to rates observed in population-based birth defect surveillance systems.

Genotoxicity studies revealed no risk due to ritonavir. Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumorigenic potential specific for these species but are regarded as of no relevance for humans.

1.3. PAXLOVID Clinical Development

The sponsor's clinical development program, as submitted in the PAXLOVID NDA (29 June 2022), included 9 completed Phase 1 Clinical Pharmacology Studies and 4 Phase 2/3 studies (2 completed and 2 ongoing at the time of the NDA submission).

In this briefing document, the phrase 'Evaluation of Protease Inhibition for COVID-19' or 'EPIC' is used as a generic term for the undertaken clinical studies with PAXLOVID.

- Study C4671005 (from herein referred to as EPIC-High Risk (HR); completed) is the pivotal Phase 2/3 study in unvaccinated adult participants with symptomatic COVID-19 with ≥1 risk factor for progressing to severe COVID-19 disease.

- Studies C4671002 (from herein referred to as EPIC-Standard Risk (SR); ongoing at time of NDA submission) and C4671006 (from herein referred to as EPIC-Post-Exposure Prophylaxis [PEP]; completed) are supportive Phase 2/3 studies.

    - EPIC-SR is in adult participants with symptomatic COVID-19 at standard risk of progressing to severe disease – comprising participants who either 1) have at least 1 risk factor for progression to severe disease and are fully vaccinated; or 2) do not have risk factors for progression to severe disease and are not vaccinated.

    - EPIC-PEP is in adult participants who were asymptomatic, were rapid antigen test negative at baseline and who were household contacts of an individual with symptomatic COVID-19.

- Study C4671026 (from herein referred to as EPIC-Peds) is an ongoing Phase 2/3 study in pediatric participants with COVID-19 who are at increased risk of progressing to severe disease.

1.4. Key Clinical Pharmacology Conclusions

Clinical pharmacology evaluations support the proposed dose of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adult patients.

- The proposed dose is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days. The commercial formulation of PAXLOVID is the same as that used in all Phase 2/3 studies.

- Nirmatrelvir is co-administered with ritonavir, a strong CYP3A4 inhibitor. The low dose of ritonavir (100 mg) is used as a PK enhancer to achieve exposures of nirmatrelvir sufficient to suppress viral replication through the entire dosing interval (ie, $C_{trough} > EC_{90}$). Ritonavir 100 mg does not exert antiviral activity against SARS-CoV-2.

- No dosage adjustment is required in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Doses of nirmatrelvir are recommended to be reduced by half to 150 mg twice daily, given with 100 mg ritonavir, in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min). The appropriate dosage for patients with severe renal impairment (eGFR <30 mL/min) has not been determined.

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

- DDI studies suggested that the interactions of PAXLOVID are mainly associated with ritonavir. Thus, for the proposed labelling, the sponsor has generally followed the guidance of the Norvir (ritonavir) label,[20] for drugs that are to be contraindicated as well as those with clinically significant drug interactions. Additionally, numerous drugs that are likely to interact with PAXLOVID but were not part of the Norvir label are also added to the label. The sponsor has also included recommendations and referrals to other product labels, for managing several potentially significant drug interactions (Table 28).

1.5. Key Efficacy Conclusions

Pivotal Study EPIC-HR

In the pivotal Phase 2/3 Study EPIC-HR, PAXLOVID significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in non-hospitalized symptomatic adult participants who were at increased risk of progression to severe disease compared to placebo. Statistically significant results from the primary and key secondary analysis showed an 89.1% relative risk reduction (-6.1% absolute difference, $p<0.0001$) and 85.8% relative risk reduction (-5.6% absolute difference, $p<0.0001$) was observed when treatment was initiated within 3 days (mITT analysis set) or within 5 days (mITT1 analysis set) of symptom onset, respectively. See Table 25 for definitions of the population analysis sets.

The results summarized below for Study EPIC-HR focuses on the broader mITT1 analysis population:

- The median time to sustained alleviation of all targeted COVID-19 signs and symptoms in the placebo group was 15 days and was reduced to 13 days in the PAXLOVID group. The hazard ratio for treatment with PAXLOVID versus placebo was 1.27 ($p<0.0001$), indicating participants in the PAXLOVID group were 27.0% more likely to achieve sustained alleviation of all targeted signs and symptoms.

- Results from the prespecified subgroup analyses of the primary endpoint by age, gender, race, and body mass index (BMI) were consistent with the overall mITT1 population.

- There were 15 deaths in the placebo group (12 in the 28-day period, 1 in the safety follow-up period through Day 34, and 2 in the long-term follow-up period [ie, through Week 24]) and none in the PAXLOVID group during the entire study period.

- COVID-19-related medical visits were less frequent in the PAXLOVID group (2.3%) compared to the placebo group (8.4%), with medical visits occurring less frequently

for PAXLOVID compared with placebo (Event Rate Ratio of 0.357, p<0.0001). This corresponds to a 73% relative risk reduction with treatment.

- The anti-viral effect of PAXLOVID was demonstrated by significant reduction of SARS-CoV-2 viral RNA levels compared with placebo, with an adjusted mean difference (SE) of 0.777 (0.081) log_{10} copies/mL reduction (~6-fold reduction) (nominal p<0.0001).

Type I error control for the primary endpoint and key secondary endpoints is described in Section 4.2.2.

Supportive Study EPIC-SR

The primary analysis result, ie, time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28 (the primary endpoint) for PAXLOVID compared with placebo, was not statistically significant, and the primary objective of Study EPIC-SR was not met.

- The median time to sustained alleviation of all targeted signs and symptoms through Day 28, was 14 days for placebo treatment compared with 13 days for PAXLOVID treatment (mITT1 analysis set [see definition Table 26] who received treatment within 5 days of symptom onset). The treatment difference for the primary endpoint was not statistically significant (log rank test p=0.515).

Furthermore, specifically in participants with at least 1 risk factor for severe COVID-19 disease who were fully vaccinated (as defined by local regulations and practices) in Study EPIC-SR (N=317 for PAXLOVID and N=314 for placebo):

- PAXLOVID reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo in vaccinated, non-hospitalized symptomatic adult participants with COVID-19 who were at high risk of progression to severe illness. PAXLOVID demonstrated a 57.6% relative risk reduction although the difference in the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 was not statistically significant (nominal p=0.197).

- 7 out of 317 PAXLOVID-treated participants (2.208%) and 17 out of 314 placebo-treated participants (5.414%) reported a COVID-19-related medical visit, corresponding to a 59.2% relative risk reduction with PAXLOVID treatment (nominal p=0.007).

1.6. Antiviral Activity, Viral Resistance, and Treatment Emergent Mutations

PAXLOVID is an effective antiviral agent showing broad anti-coronavirus activity against known SARS-CoV-2 VOC. Nirmatrelvir has shown antiviral in vitro activity against Alpha, Beta, Gamma, Lambda, Delta, and all Omicron variants that have been tested (Table 5). In EPIC clinical studies, PAXLOVID is highly effective in reducing the risk of hospitalization or death from COVID-19 and is effective in lowering nasal/nasopharyngeal (NP) viral RNA

levels in participants infected with Delta and Omicron. M^{pro} mutations identified in cell culture with reduced susceptibility to nirmatrelvir show very low prevalence post PAXLOVID EUA approval in a public domain database such as GISAID. Viral genomic surveillance of NP/nasal swabs from all participants in the EPIC clinical trials have not identified any baseline or post-dose emergent M^{pro} mutations associated with impairment of viral RNA reduction or COVID-19-related hospitalization or death. To date, PAXLOVID is effective across all VOCs and clinical resistance of treatment emergent M^{pro} mutations has not been observed.

1.7. Key Safety Conclusions from PAXLOVID Clinical Studies

Based on the totality of the safety data from undertaken clinical studies, the sponsor has determined that PAXLOVID has an acceptable safety profile that supports a positive benefit-risk assessment for use in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

The Integrated Safety Pool (ie, Studies EPIC-HR and EPIC-SR combined) which included both vaccinated and unvaccinated adult participants with at least 1 factor for progressing to severe disease and unvaccinated participants without risk factors for severe disease was the primary pool used for the interpretation of safety. AEs and SAEs were collected from the time of informed consent before participation in the study, through Day 34 (28 days after last dose of study drug [‘active collection period’]).

- The most common adverse reactions (≥1% frequency in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were Dysgeusia (5.7% and 0.4%, respectively), and Diarrhoea (2.9% and 1.9%, respectively). Additional adverse reactions identified in the clinical studies included Headache (1.5% and 1.9%, respectively) and Vomiting (0.9% in both treatment groups).
    - Based on ADR calculations Headache and Vomiting do not meet the criteria of ‘occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group’. However, based on available data and causality assessment, the sponsor has determined that these 2 AEs should remain ADRs.
- The overall incidence of participants with all-causality treatment-emergent SAEs that started on or prior to the Day 34 visit was lower in the PAXLOVID treatment group (1.6%) compared with placebo (5.2%). There were 16 deaths (14 occurred during the active safety collection period [up to Day 34]; the 2 remaining deaths occurred during the long-term follow-up period [up to Week 24]) among participants in the Integrated Safety Pool, all of which occurred in the placebo group (15 deaths were related to the disease under study, and 1 death was related to sepsis with underlying relapsed acute myeloid leukemia). The proportion of participants who discontinued from study intervention due to AEs was similar between the PAXLOVID treatment group (2.0%) and the placebo treatment group (3.2%).
- PAXLOVID treatment did not lead to an increased risk for hemodynamic AEs, inflammatory AEs, thyroid-related AEs, or hypersensitivity-related AEs and was not

associated with clinically meaningful changes in laboratory values, vital signs, or ECG results.

- In supportive Study EPIC-PEP (adult household contacts of an individual with symptomatic COVID-19), both the 5- and 10-day regimen of PAXLOVID was safe and well-tolerated.

1.8. Key Post-Marketing Safety Conclusions

It is estimated that 11,646,361 patients (8,595,340 in the US and 3,051,021 outside the US) have been exposed to PAXLOVID worldwide cumulatively from the first EUA in the US in December 2021 through 31 December 2022.

The reported post-marketing adult AEs are consistent with safety data generated from the Phase 2/3 clinical studies (EPIC-HR + EPIC-SR, and EPIC-PEP) and ADRs included in the product information.

Since the NDA submission the following label updates have been made or are proposed based on post-marketing safety surveillance:

- Anaphylaxis has been added to the sponsor's Core Data Sheet (CDS) Section 4.8, Undesirable effects, as an ADR identified post-marketing (CDS version 6, effective date 22 August 2022). The sponsor proposes to add anaphylaxis to the USPI Section 6.2, Postmarketing Experience.

- A Hypersensitivity Warning and Precaution has been added to the CDS Section 4.4 Special warnings and precautions for use (CDS version 6, effective date 22 August 2022). The sponsor proposes to update the Warning and Precaution in the USPI Section 5, Warnings and Precautions.

- Hypertension has been added to the CDS Section 4.8, Undesirable effects as an ADR identified post-marketing. The sponsor proposes to add hypertension to the USPI Section 6.2, Postmarketing Experience.

1.9. Key Post-Marketing Real World Effectiveness

Published real-world evidence from Israel, Hong Kong, and the US demonstrate that PAXLOVID is highly effective in reducing the risk of hospitalization or death from COVID-19 during the Omicron-predominant period. PAXLOVID provides an important layer of protection on top of COVID-19 vaccination for high-risk individuals.

In the US, 6 real-world studies provide supportive evidence on the high effectiveness of PAXLOVID against hospitalization or death in highly vaccinated and boosted populations at high-risk for development of severe COVID-19 (as defined by CDC criteria[19]) in the era of Omicron predominance and high seroprevalence.[21-26] In 4 studies among the general population where data on date of symptom onset were not available in the evaluation of PAXLOVID treatment either within 5 days, or any time, after the diagnosis date (rather than symptom onset date), effectiveness against hospitalization or death ranged from

approximately 45% to 60%.[21,23-25] In the only study where data about date of symptom onset was available, earlier treatment with PAXLOVID was associated with increased clinical benefit. Effectiveness when individuals were treated within 5 days of symptom onset was 80% among all patients, 83% among patients vaccinated with ≥2 COVID-19 vaccine doses, and 92% among patients vaccinated with ≥3 COVID-19 vaccine doses. Moreover, effectiveness of treatment within 5 days of symptom onset increased (from 80%) to 90% when patients were dispensed treatment on the same day as testing. In contrast, when treatment was dispensed at any time regardless of symptom timing, effectiveness was 54% among all patients, 55% among patients vaccinated with ≥2 COVID-19 vaccine doses, and 67% among patients vaccinated with ≥3 COVID-19 vaccine doses.[26] Overall, the range of relative effectiveness estimates from US real-world studies (approximately 50 to 80%) is very similar to the range of estimates seen in EPIC-SR among vaccinated high risk patients (~58%) and EPIC-HR (~86%) and provides supportive evidence for high effectiveness of PAXLOVID in the prevention of hospitalization or death under real-world use.

1.10. Benefit-Risk Conclusion

There is no approved oral antiviral therapy for the treatment of mild-to-moderate COVID-19 in patients who are at high risk for progression to severe COVID-19 including hospitalization and death. Based on the totality of the scientific evidence, PAXLOVID is effective for the treatment of COVID-19 in this population relative to placebo, regardless of vaccination status. The benefits of PAXLOVID treatment are observed through reduction in COVID-19-related hospitalization or death, reductions in viral RNA levels, alleviation, and resolution of COVID-19 related signs and symptoms, and reduction in utilization of healthcare resources among individuals with COVID-19. The clinical results are further supported by real-world studies that demonstrate PAXLOVID is highly effective in reducing the risk of hospitalization or death from COVID-19 during the Omicron-predominant period in both vaccinated (with or without a booster) and unvaccinated individuals[21,23,26] who test positive for SARS-CoV-2 and are at high risk for developing severe COVID-19 based on CDC criteria.[19] Consistent with its mechanism of action, this real-world protection has been shown across all Omicron subvariants evaluated to date, including BA.1, BA.2, BA.2.12.1, and BA.4/5.[21-26] Safety data from clinical studies and available post-marketing AE reports, show that PAXLOVID has an acceptable safety profile.

In the clinical trial setting, the occurrence of both virological and symptomatic rebound was similar between PAXLOVID treated and untreated patients, and several studies have shown that rebound is likely part of the natural course of COVID-19 and not related to treatment failure (see Section 8.1).[27,28]

Although there is a risk of drug-drug interactions with PAXLOVID therapy, amongst an estimated 8.6 million patient exposures in the US, the reporting rate is low (0.005%) and primarily represented by nonserious events that are consistent with the known safety profile. Risk mitigation activities have been implemented to inform healthcare providers about appropriate use of PAXLOVID.

The public health impacts and situational context also weigh in favor of an NDA approval of the product. Specifically, COVID-19 still causes approximately 4000–5000 hospital

admissions and 500–600 deaths each day in the US as of January 2023,[29] the vast majority of which occur in high-risk individuals who are eligible for PAXLOVID.[30] Thus, many of these hospitalizations and deaths remain preventable with prompt treatment with PAXLOVID.

Moreover, therapeutic mAbs have shown erosion of protection against continuously emerging variants, uptake of mRNA bivalent vaccines has been relatively low,[13] and mitigation measures have been largely lifted. This potentially leaves a substantial proportion of individuals at high risk of severe COVID-19 being susceptible to new emerging variants and subvariants including Omicron sublineages BQ.1 and XBB.[10,31,32]

The change from an EUA to approval of PAXLOVID under an NDA will further facilitate prescriber and patient awareness, education, and access, increasing PAXLOVID's impact on both patients and the broader healthcare system by reducing COVID-19 related medical visits, hospitalizations, and deaths.

2. BACKGROUND INFORMATION

- As of February 2023, worldwide there have been over 753 million confirmed cases of COVID-19, including 6.8 million deaths.
- Since 2020, several VOC have emerged and rapidly spread globally. Omicron, the current VOC, is distantly related to previous VOC and is of significant public health concern as it carries several mutations that were found in other VOC and were associated with increased infectivity and enhanced ability to evade the immune system.
- Given the potential for SARS-CoV-2 variants to evade the immune system despite natural infection or vaccination, there is a clear medical need for safe and effective therapeutic interventions that can reduce viral levels, decrease symptom duration and severity, and prevent the progression of infection to more severe disease, including hospitalization and death.
- PAXLOVID (nirmatrelvir [PF-07321332] tablets; ritonavir tablets) is intended for the treatment of mild-to-moderate COVID-19 in adults-who are at high risk for progression to severe COVID-19, including COVID-19-related hospitalization or death.

2.1. Therapeutic Context and Unmet Medical Need

On 04 February 2020, the Secretary of HHS determined that there was a public health emergency with significant potential to affect national security or the health and security of US citizens that involved the virus that causes COVID-19 (virus later named as SARS-CoV-2).[5] On the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 pandemic effective 27 March 2020.[7]

COVID-19 manifests with symptoms ranging from fully asymptomatic to severe disease and death. The most common manifestations are fever, cough, and shortness of breath; additional common symptoms include fatigue, myalgias, nausea, vomiting, diarrhea, headache, weakness, rhinorrhea, anosmia, and ageusia.[33,34] A wide range of complications can lead to severe illness and death, including pneumonia, acute respiratory distress syndrome, liver injury, cardiac injury, thrombosis including stroke, renal disease, neurologic disease, and sepsis.[33-38]

Given the potential for SARS-CoV-2 variants to evade the immune system despite natural infection or vaccination, there is a clear medical need for safe and effective therapeutics that can reduce viral transmission, reduce duration and severity of symptoms, and prevent the progression of infection to more severe disease, hospitalization, and death. An effective oral antiviral agent offers a convenient method of drug administration without requiring attendance at a healthcare setting. Targeting a highly conserved viral enzyme essential for coronavirus replication, provides an effective therapeutic agent against current and future

variants. Furthermore, a benefit-risk profile supportive for use in individuals with mild-to-moderate COVID-19 who are at high risk of developing severe disease (based on CDC criteria[19]) will significantly add to the armamentarium for COVID-19.

2.2. Dosage

The proposed dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days. PAXLOVID tablets can be taken without regards to meals.

Doses of nirmatrelvir are recommended to be reduced by half to 150 mg twice daily, given with 100 mg ritonavir for 5 days, when used by patients with moderate renal impairment.

2.2.1. Proposed Indication

Treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

2.3. Regulatory History

PAXLOVID has not been approved but has been authorized for emergency use by FDA under an EUA since the 22 December 2021.[39] The current authorization for PAXLOVID is for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of mild-to moderate COVID-19 and who are at high-risk for progression to severe COVID-19, including hospitalization or death. Following US EUA approval on 22 December 2021, the FDA has subsequently reissued the Letter of Authorization on 17 March 2022, 14 April 2022, 06 July 2022, 05 August 2022, 27 October 2022, and 01 February 2023.[40]

Fast-track designation was granted by the FDA on 17 February 2022 on the basis that PAXLOVID has the potential to treat a serious or life-threatening condition and fill an unmet medical need.

The NDA (217188) for PAXLOVID was submitted to the FDA on 29 June 2022. The Prescription Drug User Fee Act (PDUFA) action date is 28 May 2023.

As of February 2023, PAXLOVID has received regulatory approval or authorization in over 70 countries.

2.4. Clinical Development Program and Study Design

In this document, the phrase 'Evaluation of Protease Inhibition for COVID-19' or 'EPIC' is used as a generic term for clinical studies undertaken with PAXLOVID.

The sponsor has used the following CDC guidance (Table 1) for determining the underlying medical conditions associated with higher risk for severe COVID-19.[19]

Table 1. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19[a]

Higher Risk	Suggestive of Higher Risk	Mixed Evidence for Higher Risk
Asthma	Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2)	Alpha 1 antitrypsin deficiency
Cancer	Sickle cell disease	Bronchopulmonary dysplasia
Cerebrovascular disease	Substance use disorders	Hepatitis B
Chronic kidney, liver, or lung disease		Hepatitis C
Diabetes mellitus		Hypertension[b]
Heart conditions (eg, heart failure, coronary artery disease, cardiomyopathies)		Thalassemia
Obesity (BMI ≥30 kg/m^2)		
Primary immunodeficiencies, solid organ or hematopoietic cell transplantation, use of corticosteroids, or other immunosuppressive medications		
Smoker, current and former		

a. Refer to the CDC website for the complete list.[19]
b. Indicates underlying conditions for which there is evidence for pregnant and non-pregnant people.

The sponsor's clinical development program, as submitted in the PAXLOVID NDA (29 June 2022), included 9 completed Phase 1 Clinical Pharmacology Studies (Table 2) and 4 Phase 2/3 studies (2 completed and 2 ongoing at the time of the NDA submission; Table 3). Additional clinical studies are ongoing to further investigate PAXLOVID for the treatment of SARS-CoV-2 infection in special patient populations (Table 4).

Note: As requested by FDA, data from participants enrolled in EPIC-HR sites 1274 and 1470, EPIC-SR sites 1281 and 1488, and EPIC-PEP sites 1281 and 1483 are excluded from the efficacy, safety, and PK analysis summarized in this document and sponsor presentation materials due to GLP or data integrity issues. Conclusions on the overall effectiveness, safety, and PKs of PAXLOVID based on analyses both excluding and including these sites, remain the same.

Table 2. Clinical Pharmacology Studies Supporting PAXLOVID

Study Number	Study Title
1001	A Phase 1, randomized, double-blind, sponsor-open, placebo controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of nirmatrelvir in healthy adult participants
1008	A Phase 1, open-label, randomized, single-dose, crossover study to estimate the relative bioavailability of nirmatrelvir following oral administration of 4 different formulations relative to the commercial tablet formulation in healthy adult participants under fasted conditions
1010	A Phase 1, non-randomized, open-label study to assess the pharmacokinetics, safety and tolerability of nirmatrelvir boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function
1011	A Phase 1, non-randomized, open-label study to assess the pharmacokinetics, safety and tolerability of nirmatrelvir boosted with ritonavir in adult participants with renal impairment and in healthy participants with normal renal function
1012	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period cross-over study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of dabigatran in healthy participants
1013	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period crossover study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of midazolam in healthy participants
1014	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of carbamazepine on the pharmacokinetics of nirmatrelvir boosted with ritonavir in healthy participants
1015	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of itraconazole on the pharmacokinetics of PAXLOVID in healthy participants
1019	A Phase 1, open-label, randomized, single dose, 2-sequence, 2-period crossover study to evaluate the effect of high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir in healthy adult participants

Table 3. Completed and Ongoing Clinical Studies to Support the Safety and Efficacy Assessments for PAXLOVID (Based on NDA Submission)

Study ID	Study Title	Dose and Duration of Study Intervention and Total Duration of Study	Comparator	Total Planned Sample Size
Study 1005 [Pivotal Study EPIC-HR] NCT04960202 (Completed)	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PAXLOVID compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.	PAXLOVID administered orally q12h for 5 days. Efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24	PBO	Total ~3000 participants (LPLV: N = 2246 participants)
Study 1002 [Supportive Study EPIC-SR] NCT05011513 (Ongoing at the time of the NDA submission)	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PAXLOVID compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.	PAXLOVID administered orally q12h for 5 days. Efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24	PBO	Total ~1980 participants (Interim: N = 1153 participants)
Study 1006 [Supportive Study EPIC-PEP] NCT05047601 (Completed)	A Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study to evaluate the safety and efficacy of 2 regimens of orally administered PAXLOVID in preventing symptomatic SARS-CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19.	PAXLOVID administered orally q12h for 5 or 10 days Efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days]	PBO	Total ~2880 participants (LPLV: N = 2957 participants)

Table 4. Clinical Studies to Support the Safety and Efficacy Assessments for PAXLOVID in Special Populations

Study ID	Study Description	Dose and Duration of Study Intervention	Comparator	Total Planned Sample Size
Study 1026 [Supportive Study EPIC-Peds] NCT05261139 (Ongoing)	A Phase 2/3, interventional safety, pharmacokinetics, and efficacy, open-label, multi-center, single-arm study to investigate orally administered PAXLOVID in non-hospitalized symptomatic pediatric participants with COVID-19 who are at risk of progression to severe disease	Cohort 1 (a: ≥12 to <18 years and ≥40 kg; b: ≥6 to <12 years): PAXLOVID administered orally q12h for 5 days. Cohort 2 (weight ≥20 to <40 kg, ≥6 to <18 years): 150/100 mg PAXLOVID administered orally q12h for 5 days Cohort 3 to 5 (≥2 to <6 years; ≥1 month to <2 years; <1 month): TBD Efficacy assessments through Day 28, and a safety follow-up period through Day 34	Not applicable	Total ~140 participants
Study 1028 EPIC-SRI NCT05487040 (Ongoing)	A study to investigate PAXLOVID in participants with severe renal impairment and documented COVID-19 infection	Dose of nirmatrelvir: 300/100 mg nirmatrelvir/ritonavir QD on Day 1 followed by 150/100 mg QD on Days 2 to Day 5	Not applicable	Total ~24 participants
Study 1034 EPIC-IC NCT05438602 (Ongoing)	A double-blind, 3-arm study to investigate PAXLOVID in immunocompromised participants with COVID-19	Dose of nirmatrelvir: 300/100 mg nirmatrelvir/ritonavir administered orally q12h for 5, 10 or 15 days	Not applicable	Total ~200 participants (includes up to 50 participants with COVID-19 rebound)

Table 4. Clinical Studies to Support the Safety and Efficacy Assessments for PAXLOVID in Special Populations

Study ID	Study Description	Dose and Duration of Study Intervention	Comparator	Total Planned Sample Size
Study 1035 NCT05386472 (Ongoing)	A study to evaluate the PKs, safety, and tolerability of PAXLOVID in pregnant women with COVID-19	Dose of nirmatrelvir: 300/100 mg nirmatrelvir/ritonavir administered orally q12h for 5 days	Not applicable	Total ~45 participants
Study 1039 NCT05441215 (Ongoing)	A phase 1, multiple dose, open-label pharmacokinetic study of PAXLOVID in healthy lactating women	Dose of nirmatrelvir: 300/100 mg nirmatrelvir/ritonavir administered orally q12h (2 doses on Day 1 and a single dose on Day 2)	Not applicable	Total ~ 8 participants
Study 1042 NCT05567952 (Ongoing)	A double-blind study to investigate a repeat 5-day course of PAXLOVID compared to placebo/ritonavir in participants at least 12 years of age with rebound of COVID-19 symptoms and rapid antigen test positivity	Dose of nirmatrelvir: 300/100 mg nirmatrelvir/ritonavir administered orally q12h for 5 days	Placebo/ ritonavir 100 mg q12h	Total ~411 participants

2.5. Overview of Key Nonclinical Pharmacology Findings

2.5.1. Mechanism of Action

Nirmatrelvir is a potent and selective inhibitor of SARS-CoV-2 M^{pro}, exhibiting broad-spectrum activity across the Coronaviridae family of M^{pro} demonstrating its potential for antiviral efficacy. The critical amino acid residues involved in enzyme-inhibitor binding interactions are particularly well conserved within this family of viruses.[41]

Like other coronaviruses, SARS-CoV-2 encodes a main protease (M^{pro}) also referred to as 3C-like protease ($3CL^{pro}$).[42,43] Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of the M^{pro} is essential for viral replication.[44] M^{pro} digests the virus p1a and p1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RdRp, the helicase, and the M^{pro} itself.[45]

No close human orthologs of the coronavirus M^{pro} are known.[46] The essential functional importance in virus replication together with the absence of closely related homologues in humans, identify the M^{pro} as an attractive antiviral drug target.[47]

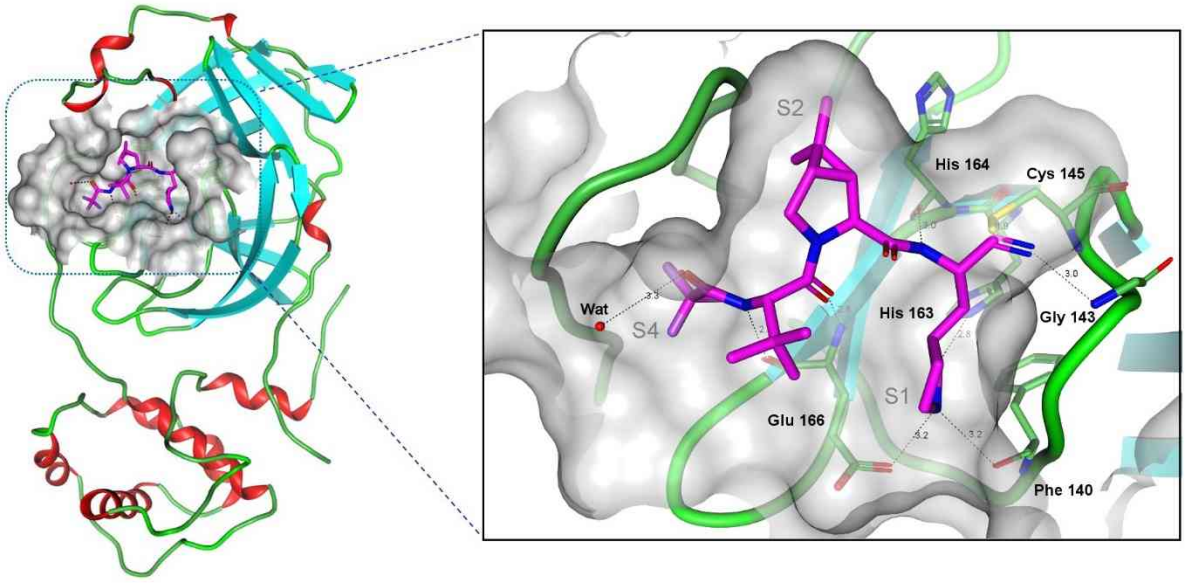
2.5.2. Antiviral Activity of Nirmatrelvir

The mechanism of action of nirmatrelvir has been demonstrated by various biochemical, crystallographic, and cell-based methods.

- Nirmatrelvir inhibited the full-length enzyme activity of SARS-CoV-2 M^{pro} with a geometric Mean IC_{50} of 0.0192 µM and a Ki of 0.00311 µM.

- Nirmatrelvir binds to the active site of SARS-CoV-2 M^{pro} and forms a covalent interaction (1.90 Å C-S bond length) with the cysteine at position 145 in the M^{pro}, as determined by the co-crystal structure (Figure 1). The binding mode of nirmatrelvir mimics the substrate binding, making numerous interactions with the protein that are analogous to enzyme-substrate contacts.[41]

Figure 1. Co-Crystal Structure of Nirmatrelvir Binding to SARS-CoV-2 M^{pro}



Nirmatrelvir binds to the substrate site of SARS-CoV-2 M^{pro} and forms a covalent interaction with the catalytic cysteine residue, Cys 145. Further, nirmatrelvir occupies the S1, S2, and S4 binding pockets of the active site. Residues that form hydrogen bond interactions (dashed lines) with the ligand are labelled

- Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM and 181 nM, respectively, as measured by virus replication after 3 days of drug exposure.

- Nirmatrelvir retains consistent and potent in vitro antiviral activity across SARS-CoV-2 variants including the currently circulating Omicron (Table 5)

Table 5. Nirmatrelvir Activity Against SARS-CoV-2 Variants

Variant	M^{pro} Mutations	Variant Fold EC_{50} Relative to WT EC_{50} (n ≥ 3) [a]
Washington	Wildtype	--
Alpha	N/A (same as WT)	~1
Beta B.1.351	K90R (99%)	~4
Delta	N/A (same as WT)	~0.5
Gamma	N/A (same as WT)	~1
Lambda	G15S (89%)	~0.6
Omicron BA.1	P132H (100%)	~0.5
Omicron variants: BA.2	P132H (100%)	~1
BA.2.12.1	P132H (100%)	~0.6
BA.4	P132H (100%)	~0.6
BA.4.6	P132H (100%)	~1.4
BA.5	P132H (100%)	~0.6

a. cell type = Vero E6 P-gp KO or Vero E6 TMPRSS2
Note: Omicron BA.2.75, BQ1.1, and XBB recently shown to be susceptible to nirmatrelvir in the literature[48-50]

2.5.3. In Vivo Activity of Nirmatrelvir

In vivo mouse models (BALB/c and 129 mouse) were used to evaluate the antiviral efficacy of nirmatrelvir (alone or in combination with ritonavir) against a mouse-adapted SARS-CoV-2, SARS-CoV-2-MA10.

Oral BID administration of nirmatrelvir rescued MA-SARS-CoV-2 infected BALB/c and 129 mice from weight loss, significantly reduced lung virus titers (~1-2 log), and ameliorated lung histopathology. Nirmatrelvir demonstrated antiviral efficacy in the BALB/c mouse-adapted model of SARS-CoV-2 while maintaining ~1xEC_{90} ([181 nM unbound concentration]) at C_{min}.[51]

In the BALB/c mouse, ritonavir alone did not demonstrate antiviral activity against in vivo virus replication and did not contribute to disease pathology, however, the combination of ritonavir and nirmatrelvir showed improved lung tissue protection compared to nirmatrelvir or ritonavir alone. This is most likely due to the increased plasma exposure levels of nirmatrelvir due to the inhibition of CYP3A-mediated metabolism of nirmatrelvir by ritonavir.

3. CLINICAL PHARMACOLOGY

- A comprehensive evaluation of the clinical pharmacology of PAXLOVID after oral administration in healthy volunteers and COVID-19 participants has been undertaken. The clinical pharmacology data were obtained from 9 clinical studies. Studies 1001, 1008, 1012, 1013, 1014, 1015, and 1019 were undertaken in healthy adult participants, one study in renally impaired participants (Study 1011) and one study in moderate hepatically impaired patients (Study 1010).
- The data summarized in this section support the recommended dose of 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 for the treatment of high-risk patients with confirmed symptomatic COVID-19.
- Selection of dosing regimen for PAXLOVID is supported by the results of the clinical pharmacology studies, Pop PK analysis, and quantitative systems pharmacology (QSP) modeling.
- Doses of nirmatrelvir are recommended to be reduced by half to 150 mg twice daily, given with 100 mg ritonavir, when used by patients with moderate renal impairment. PAXLOVID is not recommended in patients with severe renal impairment; the appropriate dosage for patients with severe renal impairment has not been determined.
- No dose adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No PK or safety data are available regarding the use of nirmatrelvir or ritonavir in patients with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment.
- Drug-drug interactions, which include CONTRAINDICATIONS and Potentially Important Drug Interactions, are described in the proposed label.

3.1. Phase 1 Studies

In the first-in-human (FIH) study, upon oral administration of single dose of nirmatrelvir at 250 and 750 mg oral suspension, enhanced with 100 mg ritonavir, the increase in exposure was less than dose proportional. Following repeat-dose of nirmatrelvir/ritonavir up to 500 mg/100 mg BID as oral suspension in fasted state, the increase in systemic exposure at steady state was less than dose proportional. Without ritonavir the single dose half-life of nirmatrelvir was about 2 hours and with ritonavir as a PK enhancer, the mean $t_{1/2}$ values for nirmatrelvir across all tested multiple dose regimens ranged between approximately 6.8 hours to 8.0 hours. Mean steady state was achieved on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 and Day 10 were similar at all doses. The absorption of nirmatrelvir co-administered with ritonavir in the fasted state occurred with the median T_{max} ranging between 0.75 hours to 2.75 hours across all doses upon single or repeat

dosing. Upon review of PK data with nirmatrelvir alone, a low dose of ritonavir 100 mg was deliberately chosen as a PK enhancer to provide sustained elevated levels of nirmatrelvir. Ritonavir 100 mg dose is commonly used for boosting human immunodeficiency virus protease inhibitors and is available as a generic product.

Using ^{19}F-NMR methodology for an absorption, distribution, metabolism, and excretion (ADME) study, the primary route of elimination of nirmatrelvir when administered with ritonavir was determined to be renal excretion of intact drug. Due to the inhibition of CYP3A4 by ritonavir, renal elimination becomes the primary route of clearance of nirmatrelvir. In this ADME study, a total of 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively. Nirmatrelvir was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. In plasma, the only drug-related entity quantifiable ^{19}F-NMR was unchanged nirmatrelvir. The protein binding of nirmatrelvir in human plasma is approximately 69%.

The relationship of nirmatrelvir concentrations versus QT interval corrected for heart rate using Fridericia's formula (C-QT analyses) was examined in healthy subjects. To achieve supratherapeutic concentrations, nirmatrelvir dose was divided into 3 doses of 750 mg each (total dose 2250 mg) administered at 0, 2 and 4 hr. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all less than 10 ms, the threshold for potential clinical concern. These data indicated that at approximately 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

A single dose food effect study conducted with the commercial formulation indicated that a high fat meal increased the AUC_{inf} and C_{max} of nirmatrelvir by approximately 20% and 61%, respectively. Since Phase 2/3 studies administered PAXLOVID without regard to meals, there are no food restrictions for administration of PAXLOVID.

3.2. Drug-Drug Interactions with PAXLOVID

In vitro studies indicate that nirmatrelvir is a substrate for CYP3A4 and human MDR1 (P-glycoprotein [P-gp]). 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. Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6, as well as an inhibitor of P-gp. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.[20]

Four clinical DDI studies were conducted with PAXLOVID. Two studies assessed the effects of itraconazole, a potent CYP3A4 inhibitor, and carbamazepine, a potent CYP3A inducer, on the pharmacokinetics of PAXLOVID. Two studies assessed the effect of PAXLOVID on midazolam, a substrate of CYP3A4, and dabigatran, a substrate of P-gp. Results of these DDI studies are provided in Table 6.

Table 6. Results of Clinical DDI Studies Conducted with PAXLOVID

Effect of Potent CYP3A4 Inhibitor and Inducer on PK of PAXLOVID		
DDI Study	**Change in Nirmatrelvir PK**	**Change in Ritonavir PK**
Itraconazole (potent CYP3A inhibitor)	↑ AUC_{tau} 39%, ↑ C_{max} 19%	↑ AUC_{tau} 21%, ↑ C_{max} 15%
carbamazepine (potent CYP3A inducer)	↓ AUC_{inf} 55%, ↓ C_{max} 43%	↓ AUC_{inf} 83%, ↓ C_{max} 74%
Effect of PAXLOVID on the PK of CYP3A4 and P-gp Substrate		
DDI Study	**Change in PK of Substrate Drug with Ritonavir alone**	**Change in PK of Substrate Drug with PAXLOVID**
Midazolam (CYP3A4 substrate)	↑ AUC_{inf} 1545%, ↑ C_{max} 287%	↑ AUC_{inf} 1330%, ↑ C_{max} 268%
Dabigatran (P-gp substrate)	↑ AUC_{inf} 69%, ↑ C_{max} 72%	↑ AUC_{inf} 94%, ↑ C_{max} 133%

These studies suggest that potent inducers can markedly reduce nirmatrelvir levels. Adding a second potent CYP3A4 inhibitor, itraconazole, on top of ritonavir used as PK enhancer minimally increased the exposure of nirmatrelvir (Table 6).

The midazolam and dabigatran DDI studies suggest that drug interactions with concomitant medications that are CYP3A4 and P-gp substrates are mainly associated with ritonavir (Table 6). Thus, the sponsor has generally followed the guidance of the Norvir (ritonavir) label,[20] for drugs that are CONTRAINDICATED as well as those with clinically significant drug interactions. In addition, several drug interactions not in the ritonavir label have been added to the label. The sponsor has also included recommendations for managing several potentially significant drug interactions (see Table 28).

3.3. Dose and Duration Selection for Phase 2/3 Studies

The dose of 300 mg/100 mg nirmatrelvir/ritonavir BID for 5 days was selected based on achieving the desired PK/PD target. Prior knowledge of viral infections suggested that maintaining nirmatrelvir plasma concentration above the EC_{90} of the virus is important for antiviral activity. Therefore, the PK/PD target chosen for dose selection was to have >90% of the patients maintain protein binding corrected trough concentrations (ie, C_{trough}) above the EC_{90} of 292 ng/mL (181 nM) starting with the first dose and to maintain that throughout the treatment duration.

Simulations were conducted based on a preliminary population PK model developed with data from FIH Study 1001 across a dose range of 100 to 500 mg nirmatrelvir with 100 mg ritonavir; key results are shown in Table 7. These simulations suggested that the PK/PD target (>90% of patients above EC_{90} after the first dose) was achieved at the 300 mg/100 mg dose of PAXLOVID. Doses of 100 mg and 200 mg were deemed inappropriate for target

attainment, while doses of 400 mg and 500 mg offered only marginal gains in target attainment.

Table 7. Predicted Ctrough Concentration of Nirmatrelvir and Percentage of Simulated Patients* Achieving Ctrough > EC90 of 292 ng/mL.

Dose of Nirmatrelvir (with 100 mg Ritonavir)	Dose Number (Day of Dosing)	Predicted C_{trough} of Nirmatrelvir			% Participants that Achieved C_{trough} ≥EC_{90}
		Median	10th Percentile	90th Percentile	
100 mg	1st (Day 1)	458	141	1018	71.5
	9th (Day 5)	852	238	2276	85.3
200 mg	1st (Day 1)	743	228	1608	85.0
	9th (Day 5)	1361	383	3575	93.4
300 mg	1st (Day 1)	987	307	2124	90.7
	9th (Day 5)	1800	498	4670	95.7
400 mg	1st (Day 1)	1209	378	2565	94.0
	9th (Day 5)	2197	605	5679	97.4
500 mg	1st (Day 1)	1417	449	2979	95.5
	9th (Day 5)	2563	704	6640	97.8

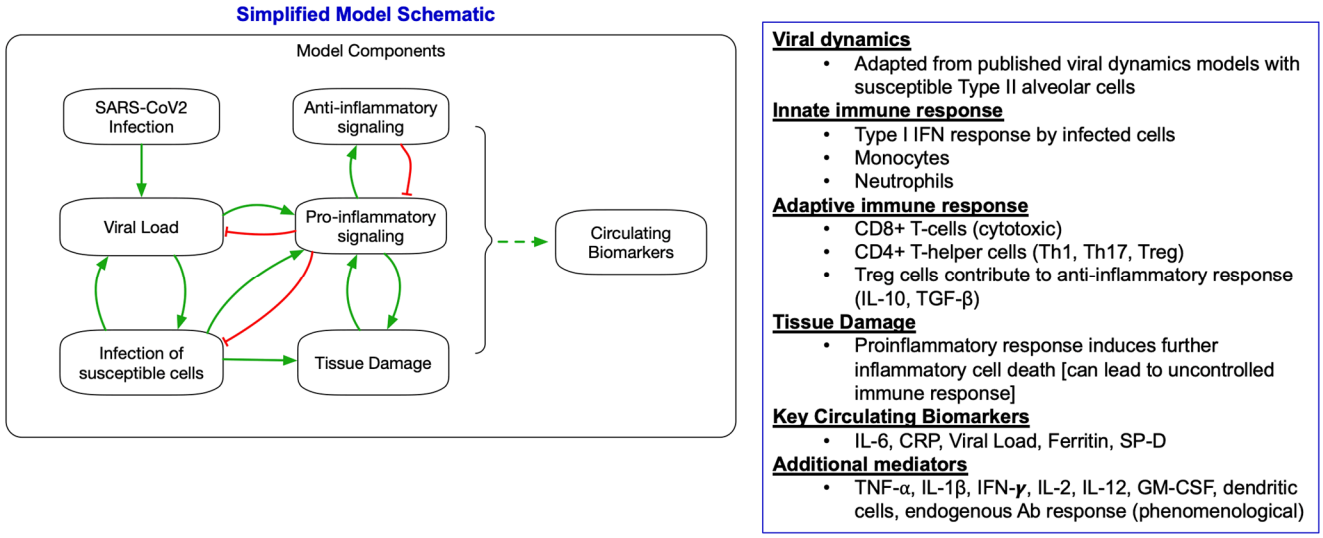
* For these simulations, the Interindividual variability was adjusted to 60% in patients as PK is generally more variable compared to healthy subjects.

The duration of the regimen was guided by a Quantitative Systems Pharmacology (QSP) model capable of describing viral dynamics in symptomatic patients infected with SARS-CoV-2. A previously published model[52] which included viral dynamics, the effect of innate and adaptive immunity, and tissue damage was utilized for QSP modeling. Parameters of the model were informed by literature data and the in vivo and in vitro PK/PD data for nirmatrelvir. Uncertainty in the model and heterogeneity in disease pathogenesis were captured by a virtual population approach.[53] The model was updated to incorporate the following:

- The observed PK profile of PAXLOVID BID
- Preclinical data on nirmatrelvir pharmacology in a mouse model of SARS-CoV-2 that was used to estimate the in vivo potency of nirmatrelvir with the QSP model
- A virtual population (N=502) that matched the placebo and treatment response of viral load and severity as reported in publicly available data[54-56]

A high-level schematic of the salient interactions accounted for in the model are depicted in Figure 2.

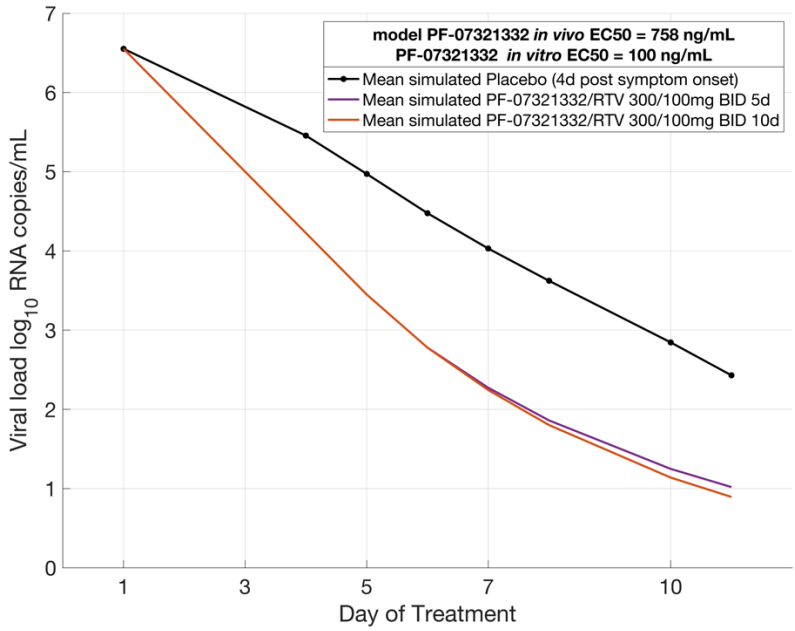
Figure 2. Simplified Model Schematic



The model describes the productive viral infection of susceptible Type II alveolar cells - infected cells together with free virus activated proinflammatory mediators of the innate and adaptive immune systems (mainly Type I interferons and CD8+ T-cells) to clear the infected cells. The activation of this proinflammatory response engages anti-inflammatory mediators such as Treg cells, IL-10, and TGF-b, which contribute to resolve the proinflammatory response. Importantly, the proinflammatory response also causes the accumulation of tissue damage because of the inflammatory death of infected and bystander alveolar cells. This can lead to positive feedback leading to a sustained immune response indicative of the more severe outcomes of COVID-19. Finally, these processes are linked to certain circulating biomarkers of interest including IL-6, C-reactive protein, ferritin, and surfactant protein-D. A more detailed description of the mechanistic interactions of the sponsor's model can be found in Dia et al.[52]

To assess the efficacy of different dosing durations, symptomatic out-patient COVID-19 population and dosing 4 days post viral load peak/symptom onset was assumed.[57] The QSP model simulations predicted that, on an aggregate level, the viral load decline with a 5-day and 10-day regimen of PAXLOVID would be similar. This suggests that 5-days of BID dosing would be sufficient for the treatment of symptomatic confirmed SARS-CoV-2 participants, with no additional benefit predicted for longer dosing (Figure 3). Hence PAXLOVID BID for 5 days was selected for further clinical evaluation in Phase 2/3 studies.

Figure 3. QSP Model Predictions for Symptomatic COVID-19 Patients



The dose and duration were subsequently confirmed by results of EPIC-HR that demonstrated the safety and efficacy of PAXLOVID administered twice daily for 5 days.

3.4. Population Pharmacokinetics

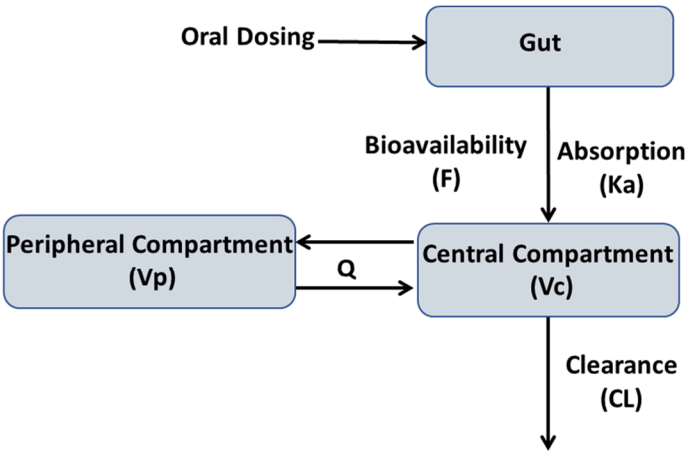
3.4.1. Final Population PK Modeling

The Final Pop PK analysis included plasma nirmatrelvir concentrations from 7 completed Phase 1 studies in healthy adult participants (serial sampling), participants with renal and hepatic impairment, and a Phase 2/3 outpatient Study EPIC-HR in non-hospitalized symptomatic adults with COVID-19 who were at increased risk of progressing to severe illness (sparse sampling). Studies varied in terms of nirmatrelvir formulation (suspension, 100 mg, and 150 mg tablets), regimen (doses and dosing frequency), fed versus fasted state, and subject population (healthy, COVID-19, hepatic, or renal impairment).

A total of 1237 participants, including 150 participants from Phase 1 studies and 1087 participants from Phase 2/3 Study EPIC-HR contributing 4404 evaluable samples were included in the final Pop PK analysis.

The final Pop PK model was a 2-compartment model with first-order elimination and first-order absorption, allometric scaling of body weight with fixed exponents to 0.75 for clearances and 1 for volumes, and dose-dependent absorption. A schematic of the model is shown in Figure 4.

Figure 4. A Schematic of the Population PK Model for Nirmatrelvir



A power function on F1 was used to describe the dose-effect on absorption, ie, relative change in F1 as a function of dose. Nirmatrelvir clearance increased proportionally to body surface area normalized creatinine clearance up to a value of ~70 mL/min/1.73 m^2 (breakpoint model). Above the estimated breakpoint of 70 mL/min/1.73 m^2, nirmatrelvir clearance was essentially independent of CLCR. With the final model, the parameter estimates at a nirmatrelvir dose of 300 mg are CL 9.09 L/h, volume of distribution (sum of V2 and V3) 70 L, and absorption rate constant (ka) 0.873 L/h. Inter-individual variability was approximately 36% for CL, 27% for V2, and 60% for ka and V3.

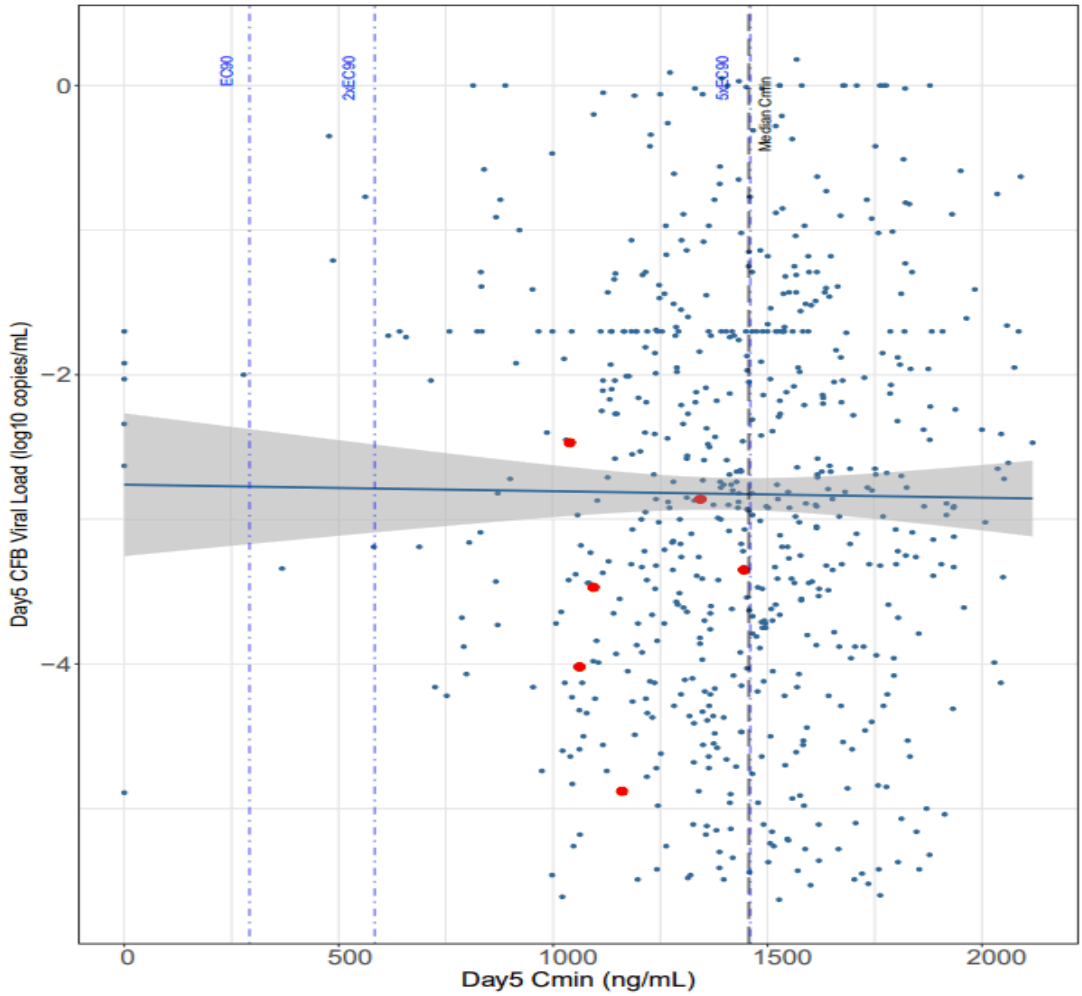
The significance of additional potential covariates, eg, age, sex, race, obesity status (baseline body mass index [BBMI] ≥30), COVID-19 infection on CL and V2; hepatic impairment and concomitant medications (CYP3A inhibitors or inducers) on CL, dose, and formulation on ka and F1 were examined. Co-administration of carbamazepine or itraconazole on nirmatrelvir CL were significant covariates. The effects of COVID-19 infection on CL (-0.341), formulation (nirmatrelvir 150 mg tablet), on F1 (-0.379), and age on nirmatrelvir V2 (power -0.425) were also significant covariates. While age was a significant covariate on V2, an approximately 25% reduction in V2 for participants aged 80 years or above is not considered to be clinically relevant. Sex, race, obesity status (BBMI ≥30), and hepatic impairment were not significant covariates on nirmatrelvir PK.

3.4.2. Pharmacokinetics in EPIC-HR

Since sparse PK sampling was performed in EPIC-HR at various times post-dose, the population PK model was used to estimate the trough concentrations of nirmatrelvir (ie, at 12 hours post dose) for patients in EPIC-HR. These model-based predictions utilized individual participant concentration data and subject covariates (e.g., age, weight, normalized creatine clearance) to predict trough concentrations for patients in EPIC-HR. These simulations showed that on Day 1 (first dose) >90% of participants in EPIC-HR were predicted to have nirmatrelvir C_{trough} above the in-vitro antiviral EC_{90} (292 ng/mL[181 nM]) starting with the first dose, thus achieving the aforementioned PK/PD target. The median C_{trough} (1417 ng/mL) on Day 5 was ~5x EC_{90}.

The exposure-response analyses of EPIC-HR participants comprised of graphical examination of PK (Day 5 predicted trough concentrations based on population PK analyses) versus PD (change from baseline in Day 5 viral RNA in NP swabs measured by RT-PCR). The PK-PD analysis population differed from that used for efficacy analyses since it consisted of participants in EPIC-HR from the active treatment arm that had both a predicted trough plasma concentration as well as VL data. A scatterplot with the associated linear regression line is shown in Figure 5. Also shown in the figure are patients from the PK-PD analysis data set that were hospitalized.

Figure 5. Scatterplot of Day 5 Change From Baseline in Viral Load Versus Predicted Day 5 C_{trough} Concentrations in EPIC-HR (based on PK/PD data set).



Participants from active treatment arm who were hospitalized are represented by red dots. Linear regression line shown in solid blue with associated 95% confidence interval in gray. Median predicted Day 5 C_{min} shown with black dashed line; EC_{90} reference lines shown with blue dot-dash lines.

Day 5 change from baseline (CFB) in VL did not show any trend with nirmatrelvir exposure across the exposure range observed in the analysis population. This is likely because nirmatrelvir exposures in participants were generally high relative to EC_{90}, with very limited

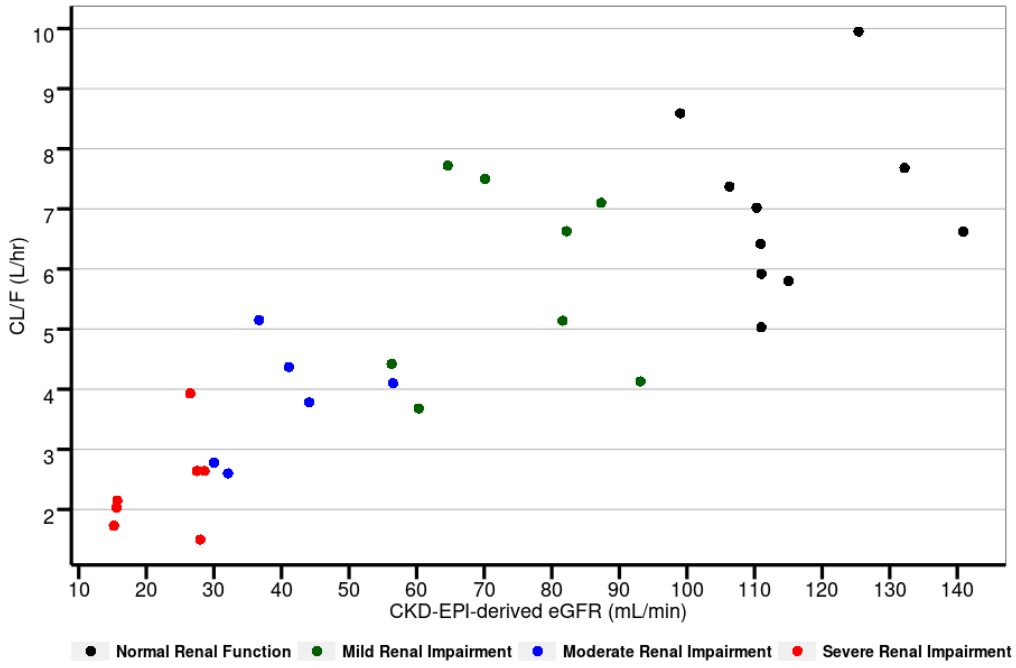
data at lower exposures. Ninety-five percent of participants had predicted nirmatrelvir trough concentrations ≥3-5 x EC_{90}.

3.5. Dosing Recommendations in Specific Populations

3.5.1. Renal Impairment

The effect of renal impairment on the PK of nirmatrelvir was examined in a single dose (100 mg nirmatrelvir with ritonavir) PK study. The exposure of nirmatrelvir in renally impaired participants increased with increasing severity of renal impairment. Compared to control group (eGFR ≥90 mL/min), the mean AUC_{inf} in mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe (eGFR <30 mL/min and not requiring dialysis) renal impaired participants was higher by 24%, 87% and 204%, respectively. Figure 6 shows the relationship between eGFR and nirmatrelvir clearance.

Figure 6. Scatter Plot of Nirmatrelvir Plasma Clearance (CL/F) Versus eGFR Following a Single Oral Dose of Nirmatrelvir/Ritonavir in Study 1011.



Nirmatrelvir clearance increased proportionally to eGFR but appeared to plateau after ~70 mL/min/1.73 m^2. Simulations were conducted to assess dose modifications in renal impairment participants that would maintain trough concentrations of nirmatrelvir similar to those in participants with normal renal functions (Table 8).

Table 8. Predicted Day 5 Trough Concentrations in Renal Impairment Patients

Renal Function	Dose (mg)	Median (10^{th}, 90^{th} percentile) Predicted C_{trough} (ng/mL)[a]	% Participants that Achieve $C_{trough} \geq EC_{90}$
Normal	300 BID	1417 (593, 2731)	98.0
Mild Impairment	300 BID	1478 (639, 2862)	98.4
Moderate Impairment	150 BID	1839 (880, 3466)	99.7

a. Based on 5000 simulated participants per group
BID=two times a day

Simulations indicated that a dose of nirmatrelvir 300 mg with ritonavir BID for 5 days in normal renal function or mild renal impairment and a dose of 150 mg with ritonavir BID for 5 days in moderate renal impairment would be expected to have >90% of simulated patients achieving trough concentrations greater than in-vitro EC_{90}.

It is noted that Phase 2/3 studies enrolled participants with eGFR ≥45 mL/min with no safety concerns in mild and moderate renal impairment participants, supporting these dose recommendations (Section 6.2.2). Therefore, no dosage adjustment is needed in patients with mild renal impairment, and those with moderate renal impairment should reduce the dose to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days.

Safety and PK assessment in severe renal impairment participants is on-going and hence PAXLOVID is currently not recommended in this patient population.

3.5.2. Hepatic Impairment

Following administration of a single 100 mg dose of nirmatrelvir with ritonavir, the exposure of nirmatrelvir in participants with moderate hepatic impairment (Child-Pugh Class B) was comparable to those in participants with normal hepatic function. Adjusted geometric mean ratios (90% CIs) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) were 98.78% (70.65%, 138.12%) and 101.96% (74.20%, 140.11%), respectively. Therefore, no dose adjustment is needed in adult patients with moderate hepatic impairment, and by inference in patients with mild hepatic impairment. No PK or safety data are available regarding the use of nirmatrelvir or ritonavir in patients with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment.

4. EFFICACY

- In pivotal Study EPIC-HR, treatment with PAXLOVID administered twice daily within 3 days of symptom onset (and no mAb treatment) significantly reduced the primary endpoint – the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28, with a relative risk reduction of 89.1% (estimated proportions of 0.752% vs 6.888%, absolute difference of -6.1%, p<0.0001) compared to placebo in non-hospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe illness at baseline (Section 4.3.1.3).
    - Overall, there were 15 deaths in the placebo group (12 in the 28-day period, 1 in the safety follow-up period through Day 34, and 2 in the long-term follow-up period [ie, through Week 24]) and none in the PAXLOVID group during the entire study period.
- In participants who were treated within 5 days of symptom onset (and no mAb treatment), PAXLOVID significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28, with a relative risk reduction of 85.8% (estimated proportions of 0.933% vs 6.571%, absolute difference of -5.6%, p<0.0001) compared to placebo (Section 4.3.1.4).
- Based on pre-specified subgroup analyses, larger risk reductions with PAXLOVID treatment compared with placebo treatment were seen in the following subgroups: participants >60 years of age, those who had viral RNA levels ≥7 $\log_{10}$ copies/ml, participants who had comorbid hypertension, or those who were SARS-CoV-2 seronegative at baseline. The relative risk reduction within the various subgroups in the mITT1 population remained between 48.36% and 95.78% (Section 4.3.1.4.1).
- The median time to sustained alleviation of all targeted COVID-19 signs and symptoms in the placebo group was 15 days and this was reduced to 13 days in the PAXLOVID group. The hazard ratio for treatment with PAXLOVID versus placebo was 1.27 (mITT1, p<0.0001), indicating participants in the PAXLOVID group were 27.0% more likely to achieve sustained alleviation of all targeted signs and symptoms compared with placebo (Section 4.3.1.5).
- COVID-19-related medical visits were less frequent in the PAXLOVID group (2.3%) compared to the placebo group (8.4%), with medical visits occurring less frequently for PAXLOVID compared with placebo (mITT1, event rate ratio of 0.357, p<0.0001). This corresponds to a 73% relative risk reduction with treatment. (Section 4.3.1.6.2).
- In supportive Study EPIC-SR, the primary analysis (time [days] to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28), was not statistically significant, and the primary objective was not met (mITT1, p=0.515). The median time to sustained alleviation of all targeted signs and symptoms through Day 28 was 14 days in placebo treatment compared with 13 days with PAXLOVID treatment (Section 4.3.2.3).
- In vaccinated high-risk participants from Study EPIC-SR, PAXLOVID treatment resulted in a non-statistically significant reduction in the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo. PAXLOVID demonstrated a 57.6% relative risk reduction in vaccinated participants who had at ≥1 risk factor for severe COVID-19 illness, although the difference in the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 was not statistically significant (nominal p=0.197) (Section 4.3.2.4).
- In an integrated analysis of data from Study EPIC-HR (unvaccinated high-risk participants) and Study EPIC-SR (vaccinated high-risk participants), PAXLOVID significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo in non-hospitalized symptomatic adult participants with COVID-19 who were either vaccinated or unvaccinated, and at increased risk of progression to severe disease, demonstrating an 83.0% relative risk reduction when treatment was initiated within 5 days of symptom onset (-4.6% absolute difference, p<0.0001) (Section 4.3.3).

4.1. Efficacy Database

Efficacy data are presented from Study EPIC-HR (completed) and Study EPIC-SR which was ongoing at the time of the NDA submission. Data for each study/pool are presented in sections linked below.

- Pivotal Study: EPIC-HR (Section 4.3.1).
- Supportive Study: EPIC-SR (ongoing at the time of NDA submission) (Section 4.3.2).
    - For Study EPIC-SR, at the time of data cutoff for the third interim analysis (100% planned enrollment through Protocol Amendment 4, data cutoff 19 December 2021) a total of 1075 participants were randomized 1:1; 544 participants to the PAXLOVID group, and 531 participants to the placebo group, and 1038 participants completed the follow-up phase.
    - For the subgroup of interest, ie, vaccinated participants who have risk factors for severe COVID-19 (mITT1 population), there were a total of 631 participants randomized 1:1; 317 participants to the PAXLOVID group, and 314 participants to the placebo group.
    - Selected efficacy results from this third interim analysis are presented within this briefing document.
- In addition, efficacy data from Study EPIC-SR and Study EPIC-HR have been integrated to support the proposed indication (Section 4.3.3). These data demonstrate the broader effectiveness of PAXLOVID in participants who were either vaccinated or unvaccinated, and at high risk of progression to severe disease.
- Supportive Study: EPIC-PEP (Section 5.1).

4.2. Phase 2/3 Efficacy Study Designs

Overall design features of the efficacy studies are summarized in Table 9.

Table 9. Listing of Phase 2/3 PAXLOVID Efficacy Studies (NDA Submission)

	Study	Number of Participants Randomized	Study Design	Population	Duration of Study Intervention and Total Duration of Study	Study Duration
Pivotal Study	1005 (EPIC-HR) (Completed)	2246	R, DB, placebo-controlled	Unvaccinated adult participants with ≥1 risk factor for severe COVID-19 illness M or F ≥18 years	PAXLOVID administered orally q12h for 5 days Efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24	24 weeks
Supportive Study	1002 (EPIC-SR) (Ongoing at time of NDA submission)	1153	R, DB, placebo-controlled	Participants at standard risk for severe COVID-19 illness Includes: 1) Unvaccinated participants with no risk factors for severe COVID-19 and 2) Fully vaccinated with at least 1 risk factor for severe COVID-19. M or F ≥18 years	PAXLOVID administered orally q12h for 5 days Efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24	24 weeks
Supportive Study	1006 (EPIC-PEP) (Completed)	2957	R, DB, DD, placebo-controlled	Participants who were asymptomatic, tested negative for SARS-CoV-2 infection and were exposed to SARS-CoV-2 by a recently diagnosed household contact M or F ≥18 years	PAXLOVID administered orally q12h for 5 or 10 days Efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days]	42 days

DB = double blind; DD = double-dummy; F = female; M = male; R = randomized.

4.2.1. Inclusion and Exclusion Criteria

4.2.1.1. EPIC-HR

Eligible participants were required to be at least 18 years old; to have confirmed SARS-CoV-2 infection and symptom onset no more than 5 days before randomization, with at least one sign or symptom of COVID-19 on the day of randomization and to have at least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19.

Key exclusion criteria were previous confirmed SARS-CoV-2 infection or hospitalization for COVID-19, anticipated need for hospitalization within 48 hours after randomization, and prior receipt of convalescent COVID-19 plasma or SARS-CoV-2 vaccine.

4.2.1.2. EPIC-SR

Eligible participants were adults ≥18 years of age with confirmed SARS-CoV-2 infection and onset of signs/symptoms of COVID-19 no more than 5 days before randomization, with at least one sign or symptom of COVID-19 on the day of randomization.

Data from participants submitted to support the New Drug Application from EPIC-SR that are summarized in this document are from participants considered to be at standard risk for severe COVID-19. Standard risk was defined as:

- Having none of the pre-defined, underlying conditions associated with increased risk of developing severe illness from COVID-19.
- Having ≥1 of the pre-defined risk factors for severe COVID-19 but was fully vaccinated against COVID-19.

For both EPIC-HR and EPIC-SR, risk factors for severe COVID-19 were defined as age ≥60 years; body mass index (BMI) >25; active smoking; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; Type 1 or 2 diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence.

Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications as defined in the protocol) was also considered a risk factor for severe COVID-19 for inclusion in EPIC-HR but was considered exclusionary (regardless of vaccination status) for EPIC-SR.

4.2.1.3. EPIC-PEP

Eligible participants were adults ≥18 years old, asymptomatic, had a negative screening SARS-CoV-2 rapid antigen test result, and were exposed to household contacts (index case) who were symptomatic (at least 1 sign or symptom considered attributable to COVID-19 per protocol) with confirmed COVID-19. Participants were randomized ≤24 hours after their negative test and ≤96 hours after collection of the index case's first positive test. Participants with risk factors (as per EPIC-HR) for severe COVID-19 were eligible to participate.

Key exclusion criteria included a history of SARS-CoV-2 infection determined by an antibody, antigen, or nucleic acid test, or any SARS-CoV-2 vaccine within 6 months of or during the screening visit.

4.2.2. Primary and Secondary Endpoints

The primary and secondary efficacy endpoints presented in this briefing document for Study EPIC-HR are described in Table 10 and all participant analysis sets are defined in the Appendix (Table 25).

Type I error was controlled at an overall rate of 0.05, by a fixed sequence testing procedure for the first three endpoints listed in the table below, followed by the Hochberg procedure for three additional endpoints including: time (days) to sustained resolution of all targeted signs/symptoms through Day 28 and number of COVID-19-related medical visits.

Table 10. Study EPIC-HR Efficacy Endpoints Presented in the Briefing Document

Type	Endpoints
Primary	
Efficacy Section 4.3.1.3	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 (mITT)[a]
Secondary	
Key Secondary Efficacy Section 4.3.1.4 Section 4.3.1.5	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 (mITT1)[b]
	• Time (days) to sustained alleviation of all targeted[d] signs/symptoms through Day 28 (mITT1)
Secondary Efficacy Section 4.3.1.6	• Time (days) to sustained resolution of all targeted[d] signs/symptoms through Day 28 (mITT1)
Secondary Efficacy Section 4.3.1.6.2	• Number of COVID-19 related medical visits through Day 28 (mITT1)
Other Secondary Endpoints	
Efficacy Section 4.3.1.6	• Proportion of participants with death (all cause) through Week 24 (mITT1)
Efficacy Section 4.3.1.6.2	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization (mITT1)
Efficacy Section 5.1	• Viral titers (viral RNA levels) measured via RT-PCR in nasal swabs over time (mITT1)[c]

a. mITT: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID 19 therapeutic mAb treatment and were treated ≤3 days of COVID 19 onset. Participants were analyzed according to the study intervention to which they were randomized.
b. mITT1: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID 19 therapeutic mAb treatment and were treated ≤5 days of COVID 19 onset. Participants were analyzed according to the study intervention to which they were randomized
c. The viral RNA assay is a validated real time RT-PCR assay. Only validated swabs were used for final analyses.
d. All targeted signs/symptoms defined as the following: Cough, Shortness of breath or difficulty breathing, Feeling feverish, Chills or shivering, Muscle or body aches, Diarrhea (loose or watery stools), Nausea (feeling like you wanted to throw up), Vomiting (throw up), Headache, Sore throat, Stuffy or runny nose.

The secondary efficacy endpoints for Study EPIC-SR presented in the briefing document are described in Table 11 and tested at a nominal alpha level. All participant analysis sets are defined in the Appendix (Table 26).

Table 11. Study EPIC-SR Efficacy Endpoints Presented in Briefing Document

Type	Endpoints
Primary	
Efficacy Section 4.3.2.3	• Time (days) to sustained alleviation of all targeted[c] signs/symptoms through Day 28 (mITT1[a])
Secondary	
Key Secondary Efficacy Section 4.3.2.4	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 (mITT1)
Efficacy Section 5.1	• Viral titers (as viral RNA levels) measured via RT-PCR in NP/nasal swabs over time (mITT1)[b]
Efficacy Section 4.3.2.4.1	• Number of COVID-19 related medical visits through Day 28 (mITT1)

a. mITT1: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention and with at least 1 postbaseline visit through Day 28. Participants were analyzed according to the study intervention to which they were randomized.
b. The viral RNA assay is a validated real time RT-PCR assay. Only validated swabs were used for final analyses.
c. All targeted signs/symptoms defined as the following: Cough, Shortness of breath or difficulty breathing, Feeling feverish, Chills or shivering, Muscle or body aches, Diarrhea (loose or watery stools), Nausea (feeling like you wanted to throw up), Vomiting (throw up), Headache, Sore throat, Stuffy or runny nose.

The secondary efficacy endpoint for Study EPIC-PEP presented in the briefing document is described in Table 12 and all participant analysis sets are defined in the Appendix (Table 27).

Table 12. Study EPIC-PEP Efficacy Endpoint Presented in Briefing Document

Type	Endpoints
Efficacy Section 5.1	Of the participants who have a positive RT-PCR result at baseline: • Viral titers (as viral RNA levels) measured via RT-PCR in nasal swabs over time (mITT1[a])[b]

a. mITT1: All participants randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline. Participants were analyzed according to the study intervention they were randomized
b. The viral RNA assay is a validated real time RT-PCR assay.

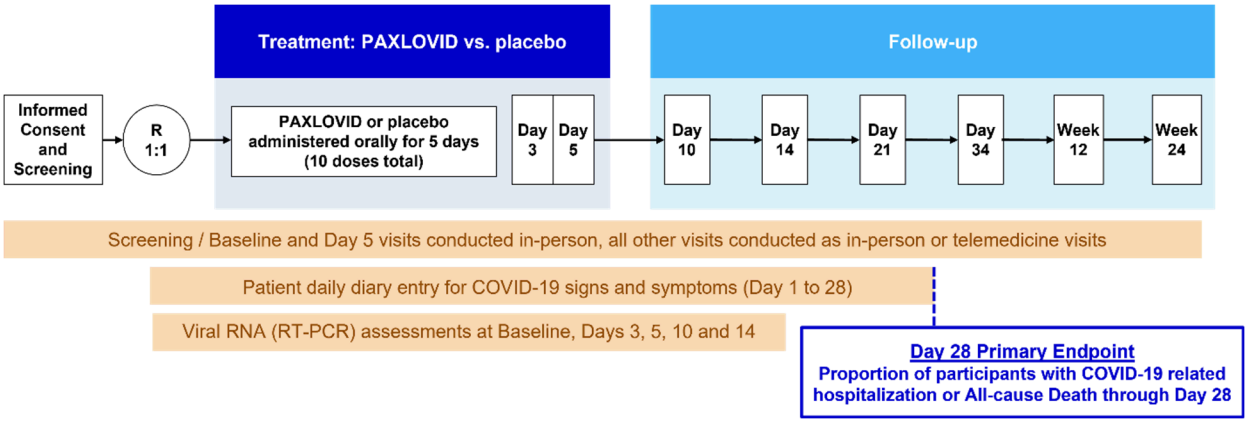
4.3. Efficacy Results

4.3.1. Pivotal Study EPIC-HR

4.3.1.1. Study Design

Eligible participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive PAXLOVID or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs based on the investigator's assessment at time of randomization. The total study duration was up to 24 weeks and included a screening period of no more than 48 hours, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24 (Figure 7).

Figure 7. Phase 2/3 Safety and Efficacy Study in Unvaccinated, Symptomatic Adult Participants with Confirmed COVID-19 who have at Least 1 Risk Factor[a] for Developing Severe COVID-19 Illness (EPIC-HR)



a. Risk Factors Include: Age ≥60, BMI >25, Medical History terms of Cigarette Smoker, Immunosuppression, Chronic kidney Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer, and Device Dependence.

4.3.1.2. Study Population

4.3.1.2.1. Disposition of Participants

Of the 2256 participants screened for entry into the study, 2113 participants were randomized, and 130 participants did not fulfil all eligibility criteria at screening. A total of 13 participants who were not screen failures were not randomized.

A total of 66 participants discontinued study intervention due to AEs, but none of those AEs caused the participant to be discontinued from the study. A total of 13 participants (all in the placebo group) discontinued from the study due to an AE.

During the follow-up (Day 34) and long-term follow-up periods, the proportion of participants who discontinued the study was similar between treatment groups. The most frequent reason for study discontinuation was withdrawal by subject.

4.3.1.2.2. Demography and Baseline Characteristics

Demographic and baseline characteristics for the FAS were similar between the PAXLOVID and placebo groups. In summary:

- Over half of the participants were male (50.6%).
- Most participants were White (70.8%), 14.9% were Asian, 9.0% were American Indian or Alaska Native, 4.2% were Black or African American, and 0.1% were Multiracial. For 0.9% of participants, race was either not reported or reported as unknown. Approximately 41% of the participants in each treatment group were Hispanic or Latino.
- The median (range) age was 45.00 (18.00, 88.00) years and 263 (12.4%) participants were 65 years of age or older at the time of randomization. The mean (SD) BMI was 29.05 (5.56) kg/m^2.

The participant population of this study reflects the patient population who are at increased risk for progressing to severe disease.

- All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with most (94.9%) participants having a qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention.
- Approximately 67% of participants received their first dose of study intervention within 3 days of symptom onset.
- Most (94.0%) participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomization.
- Participants were SARS-CoV-2 serological positive at baseline if they had evidence of antibodies to either the spike (S) or the nucleocapsid (N) antigen. Serology testing measured total immunoglobulin response.
    - Overall, 49.1% of participants were SARS-CoV-2 seropositive at baseline. The proportion of participants who were SARS-CoV-2 seropositive at baseline was balanced between treatment groups (49.9% for PAXLOVID and 48.3% for placebo).
    - 48.9% of participants were serological negative at baseline. The proportion of participants who were SARS-CoV-2 seronegative at baseline was balanced between treatment groups (48.1% for PAXLOVID and 49.7% for placebo).

- All but 1 participant had at least 1 risk factor for severe COVID-19 with over half having 2 or more prespecified risk factors.[1] Most (80.1%) participants had a baseline BMI ≥25 kg/m^2. Other common comorbidities included cigarette smoker (39.1%), hypertension (31.8%), and diabetes mellitus (10.8%).

- 61.9% participants had a baseline viral RNA concentration ≥4.0 $\log_{10}$ copies/mL and 26.9% of participants had a baseline viral RNA concentration ≥7.0 $\log_{10}$ copies/mL.

4.3.1.3. Results for Primary Endpoint

COVID-19-Related Hospitalization or Death From Any Cause (mITT)

Based on the group-sequential design and prespecified interim analysis specifications, the primary analysis result was statistically significant ($p<0.0001$), and the primary objective of the study was met and confirmed in the final analysis. PAXLOVID administered twice daily for 5 days significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in non-hospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe illness at baseline when treatment was initiated within 3 days.

- The observed event rate of COVID-19-related hospitalization or death from any cause with COVID-19 symptom onset ≤3 days from first dosing was 44 of 647 (6.801%) participants in the placebo group and 5 of 671 (0.745%) who were treated with PAXLOVID, showing an 89.0% (95% CI: 72.5% to 95.6%) relative risk reduction in observed endpoint events.

- After accounting for premature study discontinuation (ie, to include participants discontinued from study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, the estimated event rate of COVID-19-related hospitalization or death from any cause over the 28-day period among those treated with placebo was 6.888%. Among those treated with PAXLOVID, the event rate was 0.752%, a 6.137% statistically significant absolute reduction ($p<0.0001$) or an 89.1% relative reduction.

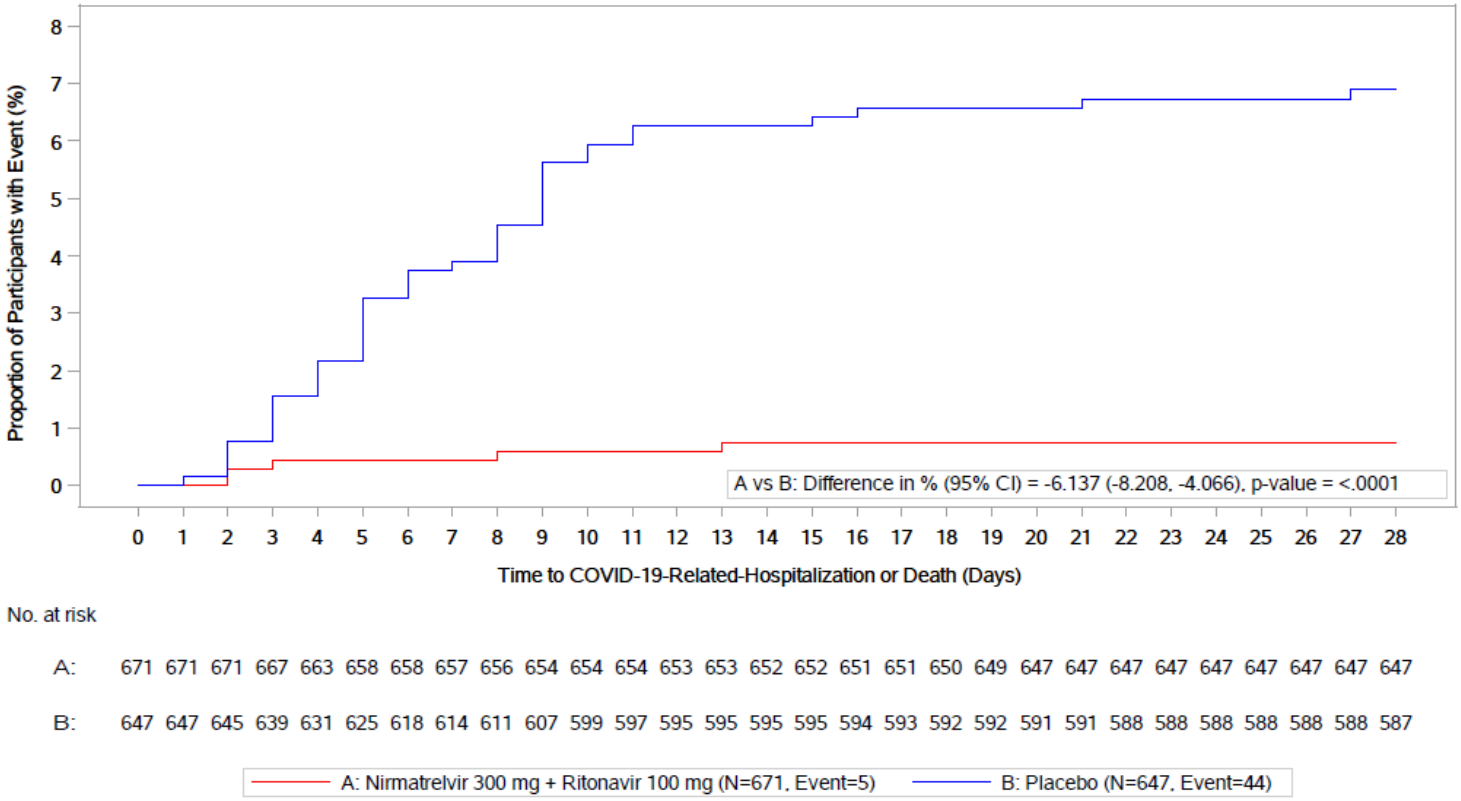
- Primary endpoint events were mostly COVID-19-related hospitalizations.

- Through Day 28, there were 9 deaths in the placebo group and none in the PAXLOVID group.

[1] Risk Factors include Age ≥ 60, BMI > 25 and Verbatims from pre-specified Medical History (Cigarette Smoker, Immunosuppression, Chronic Kidney Disease, Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence).

- Differences between PAXLOVID and placebo treated participants in the event rate of COVID-19-related hospitalization or death from any cause were observed starting from Day 3 of study treatment (Figure 8).

Figure 8. Time to COVID-19-Related Hospitalization or Death From Any Cause Through Day 28 – mITT Analysis Set



N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.
PFIZER CONFIDENTIAL SDTM Creation: 15NOV2022 (18:30) Source Data: adtte Table Generation: 20NOV2022 (20:41)
(Database snapshot date : 29APR2022) Output File: ./nda_scs/scsc4670084a_Gonzalez/adtteh_f001_mitt

4.3.1.4. Results for First Key Secondary Endpoint

The remainder of the efficacy results summarized below for EPIC-HR, are based on the broader mITT1 analysis set (ie, those participants who received treatment within 5 days of symptom onset).

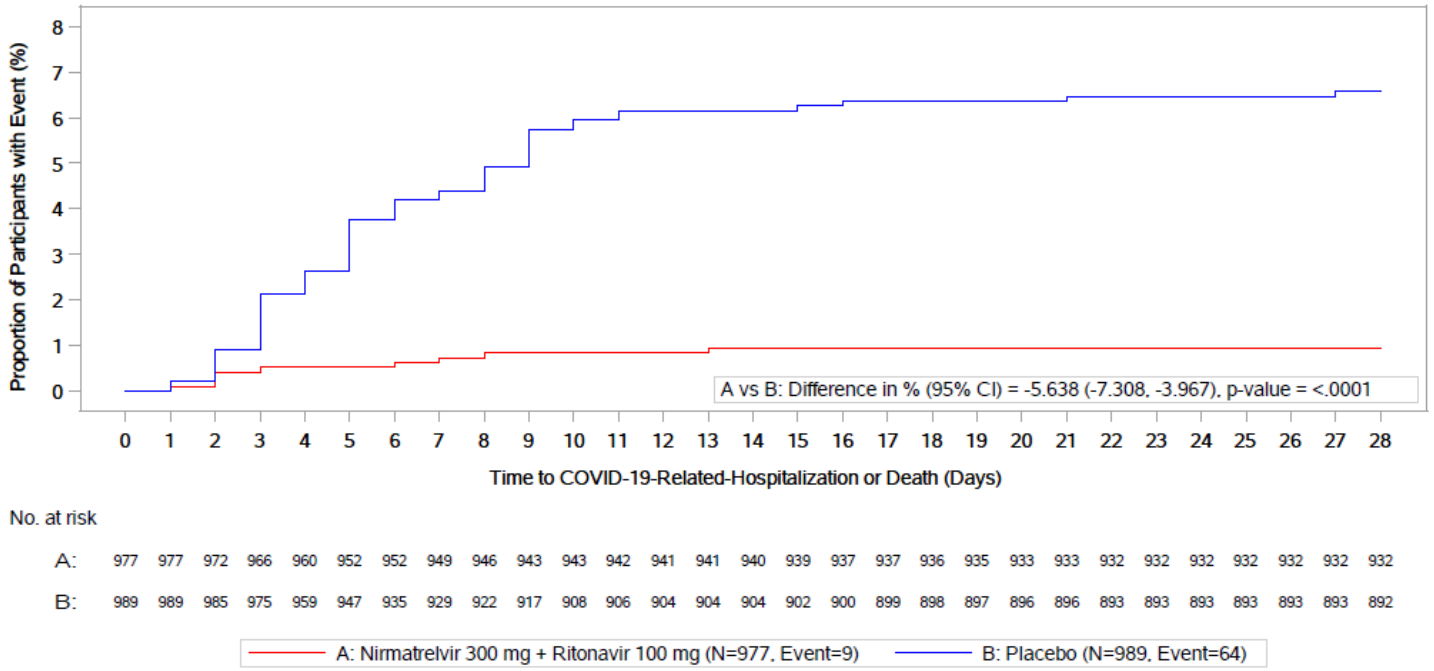
COVID-19-Related Hospitalization or Death From Any Cause (mITT1)

The observed event rate of COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set was 64 of 989 (6.471%) participants in the placebo group, and 9 of 977 (0.921%) participants in the PAXLOVID group, showing an 85.8% (95% CI: 71.6% to 92.9%) relative risk reduction in observed endpoint events.

Because the primary endpoint was statistically significant, the first key secondary endpoint was tested at an overall level of 5% as prespecified in the protocol and SAP. After accounting for premature study discontinuation (ie, to include participants who discontinued the study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID reduced COVID-19-related hospitalization or death in the mITT1 population from 6.571% to 0.933% compared to placebo, showing a 5.638% (95% CI of difference: -7.308% to -3.967%; $p<0.0001$) absolute reduction or an 85.8% relative reduction in endpoint events.

- Through Day 28, there were 12 deaths in the placebo group and none in the PAXLOVID group.
- Differences between PAXLOVID and placebo treated participants in the event rate of COVID-19-related hospitalization or death from any cause were observed starting from Day 3 of study treatment (Figure 9).

Figure 9. Time to COVID-19-Related Hospitalization or Death From Any Cause Through Day 28 – mITT1 Analysis Set



N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.

4.3.1.4.1. Results of Subgroup Analyses for First Key Secondary Endpoint

Analyses of COVID-19-Related Hospitalization or Death From Any Cause by Subgroup (mITT1 Population)

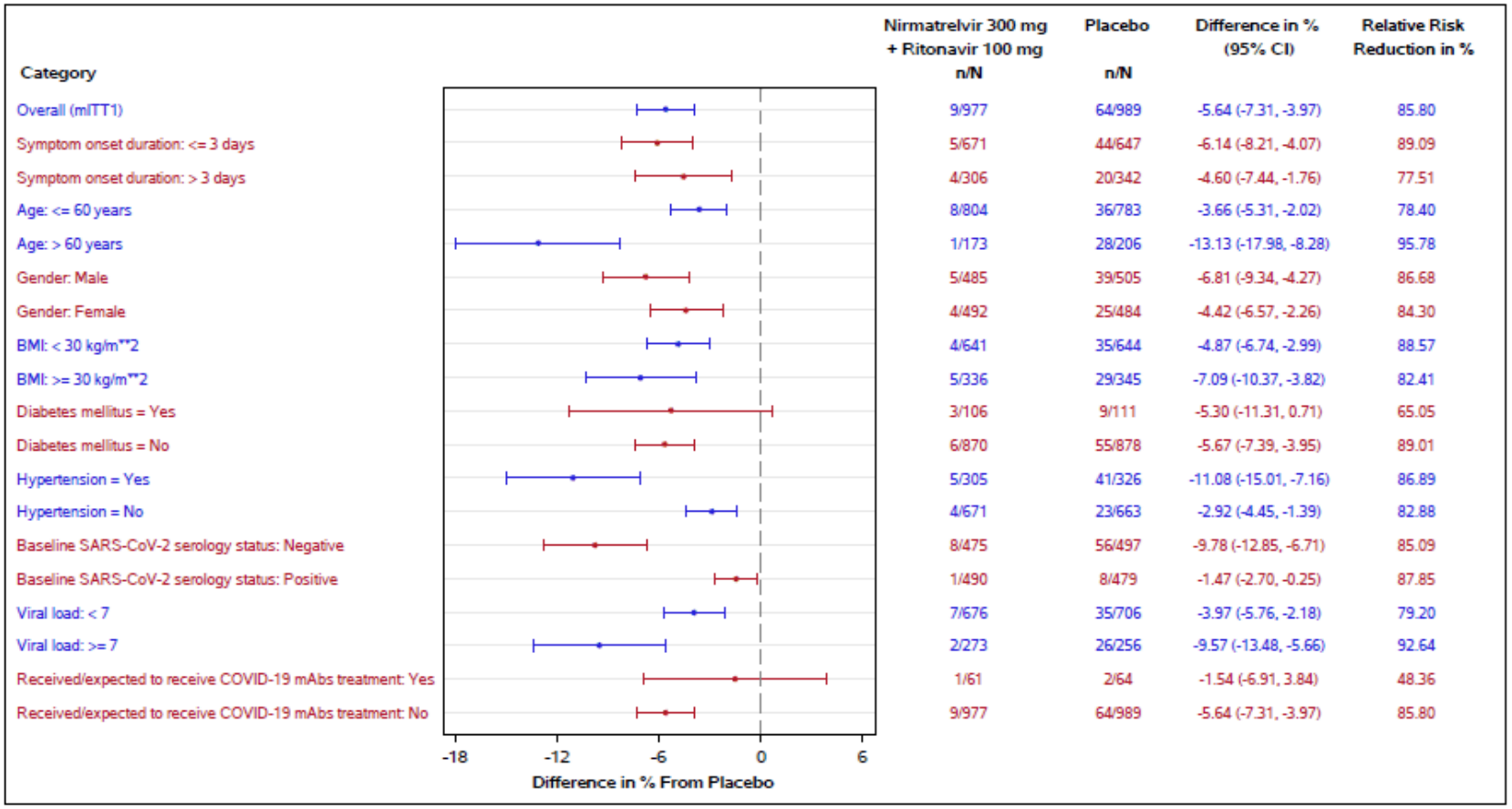
Results from Study EPIC-HR showed consistent risk reduction in COVID-19 related hospitalization or all-cause death with PAXLOVID treatment compared to placebo across prespecified participant subgroups in the mITT1 analysis set (see Figure 10). Specifically:

- Relative risk reduction in hospitalization or all-cause death in the overall mITT1 population ranged from 48.36% for those participants received/expected to receive COVID-19 mAb and up to 95.78% for those participants who were >60 years of age.

- Importantly, for participants initiating treatment within ≤3 days or >3 days of symptom onset, the analysis consistently showed a risk reduction of COVID-19 hospitalization or all-cause death with PAXLOVID treatment compared with placebo.

- The prespecified subgroup analysis of the primary endpoint in the subgroups of baseline comorbidities were consistent with the overall mITT1 population, except where either few events occurred, or a statistical test could not be performed because no participants had the event.

Figure 10. Reduction in Risk of COVID-19 Hospitalization or All-Cause Death Across Prespecified Participant Subgroups in Study EPIC-HR Through Day 28



N = number of participants in the category of the analysis set. Units for baseline Viral Load: Log10 copies/mL
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 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 risk reduction (%) = 100% × (1 - (Estimated proportion for Nirmatrelvir+Ritonavir/Estimated proportion for Placebo)).
Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.

4.3.1.5. Results for Second Key Secondary Efficacy Endpoint

Time to Sustained Alleviation of All Targeted Signs/Symptoms Through Day 28 (mITT1)

Because statistical significance was achieved in the analyses of both the primary and first key secondary efficacy endpoints, the time to sustained alleviation in all targeted signs/symptoms through Day 28 was analyzed with an alpha level of 5% in the sequential testing procedure.

Treatment with PAXLOVID significantly reduced the time to sustained alleviation of all targeted signs and symptoms through Day 28 in the mITT1 analysis set. Sustained alleviation was defined as the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent and all symptoms scored as mild or absent at study entry are scored as absent.

- The proportion of participants who achieved sustained alleviation of all targeted signs and symptoms through Day 28 was 64.909% in the placebo group, and 72.680% in the PAXLOVID group.

- The median time to sustained alleviation in the placebo group was 15 days and was reduced to 13 days in the PAXLOVID group. The hazard ratio for treatment with PAXLOVID versus placebo was 1.27 (95% CI: 1.134, 1.412; $p<0.0001$), indicating participants in the PAXLOVID group were 27.0% more likely to achieve sustained alleviation of all targeted signs and symptoms compared with placebo.

- Except for GI-related symptoms such as diarrhea and vomiting, sustained alleviation of individual targeted COVID-19 signs or symptoms occurred at a median of 1-2 days earlier in the PAXLOVID group compared with the placebo group.

4.3.1.6. Results for Secondary Efficacy Endpoints

4.3.1.6.1. Time to Sustained Resolution of Targeted COVID-19 Signs or Symptoms Through Day 28 (mITT1)

Treatment with PAXLOVID also reduced the time to sustained resolution of all targeted signs and symptoms through Day 28 in the mITT1 analysis set, compared with placebo. Sustained resolution was defined as the first of 4 consecutive days when all targeted symptoms are scored absent.

- The median time to sustained resolution in the placebo group was 19 days and was reduced to 16 days in the PAXLOVID group. The hazard ratio for treatment with PAXLOVID versus placebo was 1.20 ($p=0.0022$), indicating participants in the PAXLOVID group were 20.0% more likely to achieve sustained resolution of all targeted signs and symptoms.

- Except for GI-related symptoms such as diarrhea, vomiting, and nausea, sustained resolution of individual targeted COVID-19 signs or symptoms occurred at a median of 1-3 days earlier in the PAXLOVID group compared with the placebo group.

- Notably, a 3-day reduction in time to resolution of shortness of breath or difficulty breathing, and muscle or body aches were observed in the PAXLOVID group compared with the placebo group.

4.3.1.6.2. COVID-19-Related Health Care Utilization (mITT1)

Fewer hospitalizations were reported among those who received PAXLOVID compared with placebo (9 versus 63 participants).

- No participants in the PAXLOVID group and 9 participants in the placebo group were admitted to the ICU.

- No participants in the PAXLOVID group and 4 participants in the placebo group (FAS) required mechanical ventilation.

- Mean days of hospitalization per 100 participants was significantly reduced among PAXLOVID treated participants (8.7 days versus 76.6 days, p=0.0000).

Among hospitalized participants (FAS) with known discharge status, 100% of those who received PAXLOVID were discharged to home self-care versus 54.7% of those receiving placebo. The remaining placebo-treated participants either expired while in hospital or were discharged to home under the care of others or to a skilled nursing facility.

Through Day 34, fewer participants in the PAXLOVID group reported COVID-19-related medical visits compared to placebo.

- 2.3% (22/977) with PAXLOVID and 8.4% (83/989) of participants who received placebo reported any COVID-19-related medical visits, corresponding to a 73% relative risk reduction with treatment.

4.3.1.6.3. Death (All-Cause) Through Week 24 (mITT1)

In the mITT1 analysis set, there were 15 deaths in the placebo group and none in the PAXLOVID group through Week 24 (Table 13).

Of these, 12 deaths occurred in the 28-day period, 1 in the safety follow-up period, and 2 in the long-term follow-up period (Day 67 [related to COVID-19] and Day 96 [sepsis with underlying relapsed acute myeloid leukemia]).

Table 13. Analysis of Proportion of Participants With Death From Any Cause Through Week 24 - mITT1 Analysis Set (Protocol C4671005)

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	977	989
Participants with event, n (%)	0	15 (1.5)
p-value	<.0001	

N = number of participants in the analysis set.
P-value from the Fisher's exact test is provided due to the lack of event in the Nirmatrelvir 300 mg + Ritonavir 100 mg group.
Participants enrolled at sites 1274 and 1470 (including those switched to 1276) are excluded.

4.3.2. Supportive Study EPIC-SR

4.3.2.1. Study Design

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive PAXLOVID or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 days vs >3 to 5 days). The total study duration was up to 24 weeks and includes a screening period of no more than 48 hours, administration of study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24. Overall, The design of EPIC-SR was identical to the schedule of assessments as EPIC-HR (Figure 7) albeit with a different patient population (standard risk) and order of endpoints.

4.3.2.2. Study Population

4.3.2.2.1. Disposition of Participants

As of the data cutoff (19 December 2021), 1075 participants in the interim analysis had entered the treatment phase.

Of the 1165 participants screened for entry into the study, 1075 participants were assigned to treatment. 83 participants did not fulfil all eligibility criteria at screening. The proportion of participants who completed each phase of the study was similar between both treatment groups:

- During the treatment period, 15 participants discontinued study intervention during the treatment period due to an AE, but none of those AEs caused the participant to be discontinued from the study.
- During the follow-up and long-term follow-up periods, the proportion of participants who discontinued the study was similar for both treatment groups. The most frequent

reason for study discontinuation was withdrawal by subject. One participant in the placebo group completed the treatment phase but discontinued the study due to an AE during the follow-up.

4.3.2.2.2. Demography and Baseline Characteristics

As of the data cutoff date (19 December 2021), demographic characteristics for the mITT1 analysis set were similar between the PAXLOVID and placebo groups.

- Over half of participants were female (52.3%).
- Most participants were White (78.5%), 12.8% were Asian, 3.8% were American Indian or Alaska Native and 3.5% were Black or African American. For 1.4% of participants, Race was either not reported or reported as unknown. Approximately 43% of the participants in each treatment group were Hispanic or Latino.
- The median (range) age was 41.00 (18.00, 87.00) years and 90% of participants were under 60 years of age at the time of randomization. The mean (SD) BMI was 26.53 (5.44) kg/m^2, and approximately 49% of participants had a BMI of ≥ 25 kg/m^2 at the time of screening.

Baseline characteristics were balanced between both treatment groups, except for baseline viral RNA concentration.

- All participants had a laboratory-confirmed SARS-CoV-2 diagnosis, with 96.1% of participants having a qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention.
- Approximately 40% of participants had no risk factors. The most common comorbidities were cigarette smoking followed by hypertension and diabetes mellitus.
- Nearly half of participants reported a moderate intensity for their worst sign/symptom severity at baseline.
- 61.0% of participants were vaccinated for COVID-19.
- Participants were SARS-CoV-2 serological positive at baseline if they had evidence of antibodies to either the S or the N antigen. Serology testing measured total immunoglobulin response.
    - Overall, 73.7% of participants were SARS-CoV-2 seropositive at baseline and the proportion of participants who were SARS-CoV-2 seropositive at baseline was balanced between treatment groups. The high percentage of vaccinated participants contributed to the high proportion of baseline SARS-CoV-2 seropositivity observed.

- The mean (SD) baseline viral RNA concentration was higher in the PAXLOVID group compared with placebo: 5.19 (2.88) $\log_{10}$ copies/mL and 4.85 (2.95) $\log_{10}$ copies/mL, respectively.

- 68.1% participants had a baseline viral RNA concentration ≥4.0 $\log_{10}$ copies/mL and 31.9% of participants had a baseline viral RNA concentration ≥7.0 $\log_{10}$ copies/mL.

4.3.2.3. Results for Primary Efficacy Endpoint

Time (Days) to Sustained Alleviation of All Targeted COVID-19 Signs/Symptoms Through Day 28 (mITT1)

The primary analysis result, based on data collected and summarized through 19 December 2021, was not statistically significant, and the primary objective of the study was not met.

The median time to sustained alleviation of all targeted signs and symptoms through Day 28, was 14 days with placebo treatment compared with 13 days for PAXLOVID treatment (mITT1 analysis set). The treatment difference for the primary endpoint was not statistically significant (log rank test p=0.515).

Within the subgroup of high-risk vaccinated participants, the median time to sustained alleviation of all targeted signs and symptoms through Day 28, was 12 days for PAXLOVID and 13 days for placebo treatments. Although the analysis of median time to sustained alleviation of all targeted signs and symptoms through Day 28 did not demonstrate a significant treatment effect for the PAXLOVID versus placebo treatment groups, the time to symptom alleviation was the same or shorter for nine of eleven symptoms for PAXLOVID treatment. The most notable difference between treatment groups in the time to symptom alleviation was for shortness of breath or difficulty breathing where the time to symptom alleviation occurred three days (4 versus 7 days) sooner for PAXLOVID treatment compared with placebo treatment (respectively).

4.3.2.4. Results for Secondary Efficacy Endpoint

Proportion of Participants With COVID-19 Related Hospitalization or Death From Any Cause Through Day 28 by Subgroup of Vaccination/Risk Status (mITT1)

In a subgroup analysis of COVID-19-related hospitalization or death from any cause through Day 28 by vaccination/risk status at baseline, the risk reduction for PAXLOVID compared with placebo was -1.292% (95% CI of difference: -3.255 to 0.671), nominal p=0.197 (57.6% relative risk reduction) and -0.514% (95% CI of difference: -2.563 to 1.536), nominal p=0.6233 (35.8% relative risk reduction) in participants who were vaccinated with ≥1 risk factor at baseline, or not vaccinated without risk factors at baseline, respectively.

- The 10 participants who were vaccinated at baseline and had an event, reported at least 1 risk factor for severe illness from COVID-19 at baseline.

- The observed event rate was 7 of 314 (2.229%) participants in the placebo group, and 3 of 317 (0.946%) participants in the PAXLOVID group.

- The 5 participants who were not vaccinated and had an event, did not have any risk factors for severe illness from COVID-19 at baseline.

The rate of COVID-19 related hospitalizations or deaths through Day 28 among PAXLOVID-treated patients in the vaccinated subgroup was similar to that previously demonstrated in EPIC-HR among unvaccinated participants (0.946% and 0.921%, respectively).

4.3.2.4.1. COVID-19-Related Health Care Utilization (mITT1)

Fewer hospitalizations were reported among those who received PAXLOVID compared with placebo (5 versus 10 participants) during the first 28 days of the study.

- No participants in the PAXLOVID group and 3 participants in the placebo group were admitted to the ICU.

- Mean days of hospitalization per 100 participants was reduced among PAXLOVID treated participants (5.9 days versus 21.8 days).

Through Day 34, fewer participants in the PAXLOVID group reported COVID-19-related medical visits compared to placebo.

- 2.2% (12/540) with PAXLOVID and 4.4% (23/528) of participants who received placebo reported any COVID-19-related medical visits, corresponding to a 49.0% relative risk reduction with treatment (nominal p=0.0231).

Within the subgroup of high-risk vaccinated participants, fewer hospitalizations were reported among those who received PAXLOVID compared with placebo (3 versus 7 participants).

- No participants in the PAXLOVID group and 2 participants in the placebo group were admitted to the ICU. One of the participants who received placebo and required ICU admission also required mechanical ventilation.

- Mean days of hospitalization per 100 participants was reduced among PAXLOVID treated participants compared to placebo (6.0 days versus 29.0 days).

Within the subgroup of high-risk vaccinated participants, through Day 34, fewer participants in the PAXLOVID group reported COVID-19-related medical visits compared to placebo.

- 2.2% (7/317) with PAXLOVID and 5.4% (17/314) of participants who received placebo reported any COVID-19-related medical visits, corresponding to a 59.2% relative risk reduction with treatment.

4.3.3. Supportive Integrated Analysis of Studies EPIC-HR and EPIC-SR

Analyses of COVID-19-Related Hospitalization or Death From Any Cause Through Day 28 (mITT1)

4.3.3.1. Statistical Analysis

Efficacy analyses were performed in the mITT1 population of each study.

4.3.3.2. Efficacy Results

COVID-19-Related Hospitalization or Death From Any Cause Through Day 28 (mITT1)

An integrated analysis was conducted for COVID-19-related hospitalization or death from any cause through Day 28 using the mITT1 analysis sets from Study EPIC-SR (vaccinated high-risk participants only) and Study EPIC-HR (unvaccinated high-risk participants) (Table 14).

- The observed event rate of COVID-19-related hospitalization or death from any cause through Day 28 in high-risk participants (vaccinated or unvaccinated) who received treatment within 5 days of symptom onset was 71 of 1303 (5.449%) participants in the placebo group, and 12 of 1294 (0.927%) participants in the PAXLOVID group, demonstrating an 83.0% (95% CI: 68.8% to 90.7%) relative risk reduction in observed events.

- After accounting for premature study discontinuation (ie, to include participants who discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PAXLOVID reduced the rate of endpoint events from 5.522% to 0.939% compared to placebo, showing a 4.582% (95% CI of difference: -5.939% to -3.226%; $p<0.0001$) absolute reduction or an 83.0% relative risk reduction in endpoint events.

- Through Day 28, there were 13 deaths in the placebo group and no deaths in the PAXLOVID group.

Results from this integrated analysis were consistent with the pivotal Study EPIC-HR results. Therefore, compared with placebo, PAXLOVID significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause in non-hospitalized symptomatic adult participants with COVID-19 who were either vaccinated or unvaccinated, and who were at increased risk of progression to severe disease.

Table 14. Analysis of Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 - mITT1, Kaplan-Meier Method (Protocol C4671002 and C4671005)

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	1294	1303
Participants with event, n (%)	12 (0.927)	71 (5.449)
Participants with COVID-19 hospitalization	12 (0.927)	70 (5.372)
Participants with death	0	13 (0.998)
Average time at risk for event (Days)[a]	27.167	26.196
Average study follow-up (Days)[b]	27.360	27.170
Estimated proportion (95% CI), %	0.939 (0.535, 1.648)	5.522 (4.401, 6.917)
Difference from Placebo (SE)	-4.582 (0.692)	
95% CI of difference	-5.939, -3.226	
p-value	<.0001	

Includes pooled COVID-19 related Hospitalization and Death data from high risk participants in C4671005 and C4671002 (vaccinated + at least one risk factor). The participant with no risk factor in C4671005 is included in the table.
N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
C4671005 participants enrolled at sites 1274 and 1470 (including those switched to 1276), and C4671002 participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.

5. VIROLOGY

The antiviral effect of PAXLOVID has been demonstrated by a significant reduction in SARS-CoV-2 viral RNA concentration from baseline (Day 1) to Day 5 across all 4 Phase 2/3 Studies.

- In pivotal Study EPIC-HR, the antiviral effect of PAXLOVID was demonstrated by significant reduction in SARS-CoV-2 viral RNA levels compared with placebo, with an adjusted mean difference (SE) of 0.777 (0.081) $\log_{10}$ copies/mL reduction (~6-fold reduction) among participants treated within 5 days of symptom onset and no mAb treatment (mITT1, nominal $p<0.0001$).

- In supportive Study EPIC-SR, PAXLOVID significantly reduced viral RNA levels at Day 5 compared with placebo, with an adjusted mean difference (SE) of 0.868 (0.111) $\log_{10}$ copies/mL (~7-fold reduction) when treatment was initiated within 5 days of symptom onset (nominal $p<0.0001$).

- In supportive Study EPIC-PEP, among participants who had a positive RT-PCR test at baseline, PAXLOVID significantly reduced SARS-CoV-2 viral RNA levels compared to placebo 5 days after the initiation of treatment, with an adjusted mean difference (SE) of 1.682 (0.499) $\log_{10}$ copies/mL reduction (~48-fold reduction) for the 5-day regimen ($p=0.0010$), a 1.468 (0.477) $\log_{10}$ copies/mL reduction (~29-fold reduction) for the 10-day regimen ($p=0.0027$), and a 1.564 (0.431) $\log_{10}$ copies/mL reduction (~37-fold reduction) when the 5-day and 10-day regimen data were combined (nominal $p=0.0004$).

- Across the 3 Phase 2/3 adult studies in the PAXLOVID treatment group, the absolute change from baseline to Day 5 adjusted mean (SE) reduction in viral RNA level was 3.087 (0.067) $\log_{10}$ copies/mL for pivotal Study EPIC-HR, 3.398 (0.088) $\log_{10}$ copies/mL for supportive Study EPIC-SR, 3.410 (0.380) $\log_{10}$ copies/mL for the 5-day regimen in supportive Study EPIC-PEP, 3.196 (0.314) $\log_{10}$ copies/mL for the 10-day regimen in Study EPIC-PEP and 3.279 (0.260) $\log_{10}$ copies/mL for the 5-day and 10-day regimen combined in Study EPIC-PEP.

- PAXLOVID was efficacious in lowering viral RNA levels in participants infected with either Delta or Omicron variants.

- There were no M^{pro} mutations with known reduced susceptibility to PAXLOVID in vitro that were identified in EPIC participants at baseline or emergent that were associated with hospitalization or death. These known in vitro M^{pro} PAXLOVID resistance mutations do not appear to be increasing in frequency in public databases.

- No baseline or treatment emergent M^{pro} mutations have been associated with hospitalization or death or failed viral load response in EPIC participants

5.1. PAXLOVID Efficacy in Lowering Viral RNA Levels Across Populations and VOC

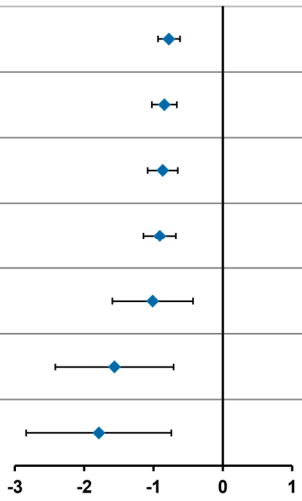
In nonclinical studies, PAXLOVID has shown efficacy across multiple VOCs including circulating Omicron variants (Table 5).

Study EPIC-HR was conducted during the latter half of 2021 and enrolled participants largely infected with Delta (98.9%). Study EPIC-SR consisted of 79.1% Delta and 18.7% Omicron, and Study EPIC-PEP consisted of 82.2 % Omicron and 17.8% Delta.

PAXLOVID was efficacious in lowering viral RNA levels in participants infected with either Delta or Omicron variants (Figure 11).

Figure 11. PAXLOVID Efficacy in Lowering Viral RNA Levels of Clinical Studies Participants Infected with Either Delta or Omicron

Study	Population/Variant	PAXLOVID n1/LS Mean	Placebo n1/LS Mean	LS Mean Diff (95% CI)	Nominal p-value
EPIC-HR (mITT1)	Overall	676/-3.087	683/-2.310	-0.777 (-0.937, -0.617)	<0.0001
	Delta	592/-3.485	580/-2.640	-0.845 (-1.024, -0.666)	<0.0001
EPIC-SR (mITT1)	Overall (iCSR)	396/-3.398	376/-2.529	-0.868 (-1.086, -0.651)	<0.0001
	Delta (LPLV)	368/-3.575	335/-2.663	-0.912 (-1.145, -0.678)	<0.0001
	Omicron (LPLV)	88/-3.534	88/-2.520	-1.013 (-1.594, -0.432)	0.0007
EPIC-PEP (mITT1)	Overall	84/-3.279	28/-1.715	-1.564 (-2.418, -0.710)	0.0004
	Omicron	56/-3.668	20/-1.878	-1.790 (-2.836, -0.745)	0.0011



Source: C4671002 iCSR Overall (mITT1): Interim snapshot Dec 2021; C4671002 Delta/Omicron: LPLV datacut; C4671005 and C4671006: LPLV datacut.
Abbreviations: CI=confidence interval; iCSR=interim clinical study report; LPLV=last patient last visit; LS=least squares, mITT1=modified intent-to-treat 1; n1 = number of participants with non-missing data in the analysis set and the covariates in the statistical model.

5.2. Nirmatrelvir Antiviral Resistance Assessments

5.2.1. M^{pro} Gene Mutation Surveillance

The sponsor has implemented a 3-tiered surveillance strategy for emergent resistant M^{pro} mutations:

- Identification and characterization of in vitro resistance mutations (ie, with in vitro reduced susceptibility to nirmatrelvir), through in vitro selection experiments and computational modeling of key residues.

- Surveillance of viral genomes in EPIC clinical data for M^{pro} mutations with in vitro resistance to nirmatrelvir and/or emergence of M^{pro} mutations that may impair clinical efficacy.

- Surveillance of viral genomes in a public domain database (GISAID) for M^{pro} mutations with in vitro resistance to nirmatrelvir and/or changes in M^{pro} mutations over time.

5.2.2. Nonclinical In Vitro Resistance Summary

Different in vitro approaches have been undertaken by the sponsor to evaluate potential nirmatrelvir resistance pathways. The sponsor followed the FDA Guidance on Antiviral Drug Development[1] as well as the COVID-19 Guidance on Developing Drug and Biological Product.[2] Testing included:

1. Evaluation of SARS-CoV-2 M^{pro} mutant enzyme activity in the presence of nirmatrelvir

2. Virus resistance selection in Vero E6 P-gp KO and A549-ACE2 cells with the same or increasing concentrations of nirmatrelvir (undertaken by the sponsor or in the literature[58,59]

3. Putative resistance substitutions identified from the above assays, dominant M^{pro} mutations from Variants of Concern, and mutations identified from EPIC HR were then tested for susceptibility to nirmatrelvir using reverse genetics.

From this work, viruses that had mutations in the M^{pro} gene were isolated from resistance selection under nirmatrelvir drug pressure or reverse engineered:

- Mutant M^{pro} viruses were not viable and could not be evaluated in the reverse engineered recombinant SARS-CoV-2 assay: Y54A, F140A, S144E, S144L, S144P, S144T, E166V and H172Y.

- SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir are presented in Table 15 (sponsor's internal data and in recent publications[58,59]). A subset of these mutations were reverse engineered into the SARS-CoV-2 virus to confirm in vitro resistance and understand viral fitness.

Table 15. M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitution (EC_{50} value fold change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (ND), S144A (2.2-2.5), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (2.1-5.5)
≥2 Substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7)

ND = no data (ie, a mutation that emerged from nirmatrelvir resistance-selection but has not been tested for EC_{50} determination in an antiviral assay).
In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold-change based on Ki values) of nirmatrelvir: Y54A (25.0), F140A (21), F140L (7.6), F140S (260), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35.0), E166G (6.2), E166V (7700), H172Y (250), A173S (4.1), A173V (16.0), R188G (38), , Q192L (29.0), Q192P (7.8), V297A (3.0), T21I+A173V (15), T21I+A173V+T304I (55), T21I+E166V (11000), T21I+L50F+A193V+S301P (7.3), T21I+S144A (20), L50F+E166V (4500), L50F+E166A+L167F (210), F140L+A173V (95), S144A+E55L (56), T304I + A173V (28), T304I + T135I (5.1), T304I + T21I + S144A (51), L50F + F140L + L167F + T304I (190), and H172Y+P252L (180). The clinical significance of these substitutions is unknown.

Most single M^{pro} mutations and some double mutations identified with reduced susceptibility to nirmatrelvir resulted in an EC_{50} shift of less than ~5-fold compared to wild type SARS-CoV-2. These mutations remain susceptible to remdesivir (sponsor internal data and literature[58,59]). Virus containing the single E166V mutation (see next section) shows the greatest reduction in susceptibility to nirmatrelvir and appears to have a replication defect since it either could not be generated or had a very low virus titer.[59]

The clinical significance of these in vitro resistant M^{pro} mutations needs to be further understood particularly in the context of the high nirmatrelvir clinical exposure (≥5x EC_{90}) achieved by PAXLOVID. Thus far, such mutations have not been identified as TEMs associated with hospitalization in the EPIC clinical studies. Additionally, the sponsor has reviewed data submitted to GISAID. As of 31 December 2022, E166V as a single M^{pro} mutation did not occur in any of the ~13 million isolates and was only found in 16 out of ~13 million isolates when in combination with other M^{pro} mutations.

Resistance studies have also provided evidence for cross resistance to nirmatrelvir by other protease inhibitors.[58-60]

5.2.3. Clinical Emergent Resistance Summary

In the EPIC clinical studies, viral genomic sequencing was conducted on all NP/nasal swabs with sufficient viral RNA levels to enable sequencing (≥3 log_{10} copies/mL, [excluding EPIC-HR sites 1274, 1470, EPIC-SR sites 1281, 1488, 1157, 1197 (2022 enrollees), and EPIC-PEP sites 1281, 1483]).

No baseline or post-dose emergent M^{pro} gene or cleavage mutations for EPIC participants on treatment were associated with COVID-19-related hospitalization or death or abnormal viral RNA clearance (eg, viral rebound).

A short list of M^{pro} mutations have been identified in vitro as having reduced susceptibility to nirmatrelvir (termed in vitro resistant mutations [Table 15]). Only one M^{pro} in vitro resistant mutation, E166V, was classified as treatment emergent and with an allelic frequency ≥10% in EPIC participants. E166V was identified in three EPIC-HR participants treated with PAXLOVID. One of these occurrences was in a participant with a baseline L50F mutation leading to the combination mutation of L50F + E166V. One of the three participants with the single mutation showed a transient viral rebound at Day 10 that resolved by Day 14. All three participants with the E166V mutation successfully cleared virus by Day 14 and none of the 3 participants experienced COVID-19-related hospitalization. Thus, the clinical significance of E166V remains unknown. To date, there are no clear signals of emergent M^{pro} resistance mutations to PAXLOVID.

COVID-19 has been associated with both symptomatic and viral RNA rebounds.[61,62] Such COVID-19 rebounds have been observed in studies in both placebo and PAXLOVID treated participants. Mutational surveillance of rebound participants in the sponsor's EPIC studies has not identified any M^{pro} or cleavage mutations associated with rebound. Please see Section 8.1 for further discussion on COVID-19 rebound.

In summary, there have been no clear signals of emergent resistant mutations to PAXLOVID that are associated with clinically meaningful endpoints such as viral rebound, recurrence of severe disease or COVID-19-related hospitalization.

Monthly clinical viral genomic surveillance of EPIC participants and public domain data will continue while PAXLOVID is under an EUA to monitor for emergence of viral resistant strains.

6. SAFETY

- PAXLOVID twice daily over a 5-day treatment period has an acceptable safety profile that supports a positive benefit-risk assessment for use in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
- The overall safety profile of PAXLOVID is based on safety data from ~6000 participants (across 13 clinical studies, including 4 Phase 2/3 studies and 9 Phase 1 studies (Section 6.1.2.1). The 5-day regimen of PAXLOVID was safe and well-tolerated across all studies. In addition, the 10-day regimen of PAXLOVID in Study EPIC-PEP, was safe and well-tolerated (Section 6.2.2).
- The most common adverse reactions (≥1% frequency in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were Dysgeusia (5.7% and 0.4%, respectively), and Diarrhoea (2.9% and 1.9%, respectively). Additional adverse reactions identified in the clinical studies included Headache (1.5% and 1.9%, respectively) and Vomiting (0.9% in both treatment groups) (Section 6.2.1.5).
- There were 16 deaths among participants in the Integrated Safety Pool, all of which occurred in the placebo group (15 related to disease under study; 1 death reported as sepsis with underlying relapsed acute myeloid leukemia) (Section 6.2.1.3).
- In the Integrated Safety Pool, the overall incidence of participants with all-causality treatment-emergent SAEs that started on or prior to the Day 34 visit was lower in the PAXLOVID treatment group (1.6%) compared with placebo (5.2%) (Section 6.2.1.2).
- In the Integrated Safety Pool, the proportion of participants who discontinued from study intervention due to an AE was similar between the PAXLOVID (2.0%) and placebo (3.2%) treatment groups (Section 6.2.1.4).
- PAXLOVID treatment did not lead to an increased risk for hemodynamic AEs, inflammatory AEs, thyroid-related AEs, or hypersensitivity-related AEs, was not associated with clinically meaningful changes in laboratory values, vital signs, or ECG results, and does not have the characteristics for being abused (Section 6.2.2).
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) or in patients with severe hepatic impairment (Section 6.2.2).
- It is estimated that 11,646,361 patients have been exposed to PAXLOVID worldwide cumulatively from the first EUA in the US in December 2021 through 31 December 2022. (Section 6.3). ADRs of anaphylaxis, hypersensitivity, nausea, abdominal pain, malaise, and hypertension have been identified post-marketing.
- The reported post-marketing adult AEs are consistent with safety data from the Phase 2/3 clinical studies (EPIC-HR+EPIC-SR and EPIC-PEP) and ADRs included in the product information.

6.1. Evaluation of Safety

6.1.1. Safety Database

The overall safety profile of PAXLOVID is based on safety data (as of 27 May 2022) from ~6000 participants (3608 PAXLOVID treated) across 13 clinical studies, including 4 Phase 2/3 studies (2 completed, 2 ongoing at the time of NDA submission) and 9 Phase 1 studies (all completed).

6.1.2. Approach to the Assessment of Safety – Clinical Studies

Primary Pool Used for the Interpretation of Safety

The Integrated Safety Pool (Phase 2/3 Studies EPIC-SR + EPIC-HR) was the primary pool used for interpretation of safety.

- Safety data from Study EPIC-SR (ongoing at time of NDA submission) for all participants enrolled through the data cut-off 19 Dec 2021 (1075 participants) was integrated with safety data from completed Study EPIC-HR (2113 participants) as both studies evaluated a 5-day treatment regimen in patients with symptomatic COVID-19 (see Study EPIC-HR schematic Figure 7). The appropriate pooling of safety data across studies provides a more precise estimate of the overall treatment effect, the treatment effect for safety endpoints that occur infrequently and any variation in treatment effect across sub-populations of clinical relevance. AEs and SAEs were collected from the time of informed consent before participation in the study, through 28 days after last dose of study drug, or Day 34 ('active collection period'). For both studies, the safety assessments through Day 34, the primary completion date (PCD; TEAE defined) were included.

  Analyses were performed in the safety analysis set (SAS) population, consisting of all randomized participants from Studies EPIC-HR and EPIC-SR who received at least 1 dose of study intervention. Participants were analyzed according to the intervention they received. Participants who were randomized but not treated were excluded from the safety analyses.

Supportive Safety Information for Safety Conclusions

- Safety data (through Day 38 [active AE reporting period]) from Phase 2/3 Study EPIC-PEP provides supportive information for safety conclusions.
  - Safety data from Study EPIC-PEP were not integrated with safety data from Studies EPIC-HR and EPIC-SR due to the different treatment durations being investigated (5 or 10 days) and the different population enrolled in Study EPIC-PEP ie, healthy adult household contacts of individuals with COVID-19. Safety data from the EPIC-PEP population was evaluated to provide supportive information for safety conclusions. A summary of safety data from Study EPIC-PEP is provided in Section 6.2.2).

- Safety data from the 9 Phase 1 clinical pharmacology studies were reported in the individual CSRs were not included in the integrated analyses. These studies included relatively low numbers of participants and the majority were single dose studies in healthy volunteers or participants without COVID-19.

Labelling – ADR Calculations

- For the purposes of labelling, data from both the Integrated Safety Pool (Study EPIC-HR and Study EPIC-SR and Study EPIC-PEP were used to determine ADRs frequency for PAXLOVID (Section 6.2.1.5).

6.1.2.1. Population Exposure

- As of 27 May 2022, there have been 3608 participants exposed to PAXLOVID across the clinical development program.[2,3]

- In the Integrated Safety Pool (Studies EPIC-HR and EPIC-SR) a total of 1578 participants with COVID-19 were exposed to PAXLOVID. Treatment duration for Studies EPIC-HR and EPIC-SR was 5 days.

- In Study EPIC-PEP, as of the primary completion date (12 April 2022) a total of 1823 adult household contacts of individuals with COVID-19 were exposed to PAXLOVID. Treatment duration for Study EPIC-PEP was 5 days (912 participants) or 10 days (911 participants).

- Across the Phase 1 studies, a total of 127 participants were exposed to a single dose and 77 participants exposed to multiple doses of study intervention.

6.1.2.2. Participant Demographics and Other Characteristics

Demographic and baseline characteristics for the Integrated Safety Pool were similar between the PAXLOVID and placebo groups.

- 49.5% of participants were male and 38.1% of participants were from the US.

- The majority (73.5%) of participants were White; 14.1% were Asian, 7.3% were American Indian or Alaska Native, 3.9% were Black or African American, and <0.1% were Multiracial. Race was not reported, or unknown in the remaining 1.1% of participants. Approximately 42% of the participants in each treatment group were Hispanic or Latino.

[2] All randomized participants are considered as independent participants.

[3] Safety data from an additional 36 participants from Study EPIC-Peds are included in this document (data snapshot: 16 Nov 2022)

- The median (range) age was 43.00 (18.0, 88.0) years and 324 (10.3%) participants were 65 years of age or greater at the time of randomization. The mean (SD) BMI was 28.20 (5.64) kg/m^2.

Baseline characteristics were balanced between both treatment groups.

- All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with most (95.3%) participants having a qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention.

- 69.2% of participants received their first dose of study intervention within 3 days of symptom onset.

- 20.6% of participants had received a COVID-19 vaccine. As prior vaccination against SARS-CoV-2 was exclusionary in Study EPIC-HR, vaccination status was not collected in Study EPIC-HR therefore this percentage represents data from Study EPIC-SR only.

- 40.9% of participants were serological negative at baseline (no evidence of antibodies to either the spike (S) or nucleocapsid (N) antigen).

- 86.4% of participants had at least 1 protocol-defined risk factor for severe COVID-19 with almost half having 2 or more prespecified risk factors. Most (69.5%) participants had a baseline BMI ≥25 kg/m^2. Other frequently reported comorbidities in at least 10% of participants in either treatment group present at the start of the study were cigarette smoker (985 [31.2%]), hypertension (824 [26.1%]), and diabetes mellitus (292 [9.2%]).

- 64.2% participants had a high baseline viral RNA level (≥4.0 $\log_{10}$ copies/mL) and 28.8% of participants had a very high baseline viral RNA level (≥7.0 $\log_{10}$ copies/mL).

6.1.2.3. Patient Evaluation and Disposition

In the Integrated Safety Pool SAS, a total of 1578 participants received PAXLOVID, and 1581 participants received placebo.

A total of 81 participants discontinued study intervention due to AEs, but none of those AEs caused the participant to be discontinued from the study. A total of 14 participants (all in the placebo group) discontinued from the study due to an AE (Table 16). The 14 participants who discontinued from study due to an AE were those who had an AE resulting in death.

The proportion of participants who completed the safety follow-up phase (Day 34) was similar between treatment groups (94.7% and 94.2% in the PAXLOVID and placebo treatment groups, respectively). The most common reason for discontinuation in either treatment group was Withdrawal by subject.

All participants in both treatment groups entered the long-term follow-up phase. At the data cut-off date, 61.3% participants had completed the long-term follow-up. The proportion of participants who discontinued the long-term follow-up was similar between treatment groups (5.8% and 6.6% in the PAXLOVID and placebo treatment groups, respectively). The most common reason for discontinuation was Withdrawal by subject.

6.2. Safety Results

6.2.1. Overview of Adverse Events

In the Integrated Safety Pool, the proportion of participants with all-causality TEAEs that started on or prior to the Day 34 visit was comparable between treatment groups (Table 16).

- Most of the all-causality TEAEs experienced by participants in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity.
- The proportion of participants with all-causality severe (Grade 3) or potentially life-threatening (Grade 4) TEAEs was lower in the PAXLOVID group compared with the placebo group.
- The proportion of participants with all-causality SAEs was lower in the PAXLOVID group compared with the placebo group.
- No participants in the PAXLOVID group experienced an AE resulting in death (Grade 5) compared to 14 (0.9%) participants in the placebo group.
- No participants in the PAXLOVID group discontinued from study due to an AE. In the placebo group, the 14 participants who discontinued from study due to an AE were those who had an AE resulting in death.
- The proportion of participants who discontinued study intervention due to an AE was low and similar between both treatment groups.

Table 16. Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set (Protocol C4671002 and C4671005)

Number (%) of Participants	Nirmatrelvir 300 mg + Ritonavir 100 mg n (%)	Placebo n (%)
Participants evaluable for adverse events	1578	1581
Number of adverse events	685	743
Participants with adverse events	354 (22.4)	382 (24.2)
Participants with serious adverse events	26 (1.6)	82 (5.2)
Participants with Maximum Grade 3 or 4 adverse events	60 (3.8)	111 (7.0)
Participants with Maximum Grade 5 adverse events	0	14 (0.9)
Participants discontinued from study due to adverse events[a]	0	14 (0.9)
Participants discontinued study drug due to AE and continue study[b]	31 (2.0)	50 (3.2)
Participants with dose reduced or temporary discontinuation due to adverse events	5 (0.3)	6 (0.4)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
C4671005 participants enrolled at sites 1274 and 1470 (including those switched to 1276), and C4671002 participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.

The proportion of participants with treatment-related TEAEs that started on or prior to the Day 34 visit was higher in the PAXLOVID group (8.1%) compared with the placebo group (4.2%).

- The overall numbers of participants with treatment-related severe (Grade 3) or potentially life threatening (Grade 4) TEAEs or SAEs were low (≤0.4%) and comparable between treatment groups.
- No participants experienced a treatment-related AE resulting in death (Grade 5).
- The proportion of participants who discontinued study intervention due to a treatment-related AE was low (≤1.0%) and similar between both treatment groups.

6.2.1.1. Most Frequent Adverse Events

In the Integrated Safety Pool, the overall incidence of all-causality TEAEs that started on or prior to the Day 34 visit was comparable between treatment groups (Table 16).

- Most of the all-causality TEAEs experienced by participants in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. Fewer participants in the PAXLOVID group reported severe events (Grade 3) or potentially life-threatening events (Grade 4) compared with the placebo group.

- There were no deaths related to an AE (Grade 5) in the PAXLOVID group compared with 14 (0.9%) deaths in the placebo group.

- The most frequently reported TEAEs by PT in the PAXLOVID group (≥1%) were Dysgeusia (4.9%), Diarrhoea (3.4%), Nausea (2.0%), Alanine aminotransferase increased (1.9%), Fibrin D dimer increased (1.8%), Headache (1.1%), Vomiting (1.4%), Creatinine renal clearance decreased (1.2%), and Aspartate aminotransferase increased (1.1%) (Table 17).

    - Of these, Dysgeusia, Diarrhoea, and Vomiting, were reported at a higher frequency in the PAXLOVID group compared with the placebo group (Table 17). These AEs were nonserious, mostly mild (Grade 1) to moderate (Grade 2) in severity and led to few discontinuations from study intervention: 4 participants, 3 participants, and 5 participants, respectively.

- In addition, the following AEs occurred at a lower frequency (<1%) but were reported more frequently (≥5 participant difference) in the PAXLOVID treatment group than the placebo treatment group:

    - Myalgia (7 [0.4%] and 1 [0.1%] participants in the PAXLOVID and placebo group, respectively),

    - Hypertension (8 [0.5%] and 4 [0.3%] participants in the PAXLOVID and placebo group, respectively),

    - Chills (5 [0.3%] and 0 [0%] participants in the PAXLOVID and placebo group, respectively),

    - Product after taste (5 [0.3%] and 0 [0%] participants in the PAXLOVID and placebo group, respectively).

Table 17. Decreasing Frequency of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) in 1% or Greater - Safety Analysis Set (Protocol C4671002 and C4671005)

System Organ Class and MedDRA v24.1 Preferred Term	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1578) n (%)	Placebo (N=1581) n (%)
With any adverse event	354 (22.4)	382 (24.2)
INVESTIGATIONS	122 (7.7)	145 (9.2)
Activated partial thromboplastin time prolonged	12 (0.8)	18 (1.1)
Alanine aminotransferase increased	30 (1.9)	35 (2.2)
Aspartate aminotransferase increased	17 (1.1)	18 (1.1)
Creatinine renal clearance decreased	19 (1.2)	20 (1.3)
Fibrin D dimer increased	28 (1.8)	36 (2.3)
NERVOUS SYSTEM DISORDERS	108 (6.8)	39 (2.5)
Dysgeusia	78 (4.9)	3 (0.2)
Headache	18 (1.1)	19 (1.2)
GASTROINTESTINAL DISORDERS	106 (6.7)	87 (5.5)
Diarrhoea	53 (3.4)	32 (2.0)
Nausea	32 (2.0)	35 (2.2)
Vomiting	22 (1.4)	20 (1.3)
INFECTIONS AND INFESTATIONS	35 (2.2)	100 (6.3)
COVID-19 pneumonia	12 (0.8)	50 (3.2)
Pneumonia	4 (0.3)	20 (1.3)

Participants are only counted once per treatment per event.
Totals for the number of participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report 2 or more different adverse events within the higher level category.
Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.1 coding dictionary applied.
C4671005 participants enrolled at sites 1274 and 1470 (including those switched to 1276), and C4671002 participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.

6.2.1.2. Serious Adverse Events

In the Integrated Safety Pool, the overall incidence of participants with all-causality treatment-emergent SAEs that started on or prior to the Day 34 visit was lower in the PAXLOVID treatment group (1.6%) compared with placebo (5.2%).

- The most frequently reported SAEs in the PAXLOVID group (≥2 participants) were COVID-19 pneumonia, COVID-19, and Pneumonia and were reported more frequently in the placebo group than in the PAXLOVID group. All of these SAEs were considered related to the disease under study; none of these SAEs were considered by the investigator to be related to study intervention (Table 18).

Table 18. Summary of Treatment-Emergent Serious Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671002 and C4671005)

Number of Participants Evaluable for AEs	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1578)	Placebo (N=1581)
Number (%) of Participants: by Preferred Term	**n (%)**	**n (%)**
With any adverse event	26 (1.6)	82 (5.2)
COVID-19 pneumonia	10 (0.6)	44 (2.8)
COVID-19	2 (0.1)	8 (0.5)
Pneumonia	2 (0.1)	13 (0.8)
Abscess	1 (0.1)	0
Brain stem stroke	1 (0.1)	0
Chest discomfort	1 (0.1)	0
Creatinine renal clearance decreased	1 (0.1)	2 (0.1)
Dyspnoea	1 (0.1)	3 (0.2)
Electrolyte imbalance	1 (0.1)	0
Facial paralysis	1 (0.1)	0
Haemoglobin decreased	1 (0.1)	0
Hepatic enzyme increased	1 (0.1)	0
Hepatic mass	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0
Osmotic demyelination syndrome	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
Palpitations	1 (0.1)	0
Pneumonia aspiration	1 (0.1)	0
Respiratory distress	1 (0.1)	0
Sepsis	1 (0.1)	1 (0.1)
Acute respiratory failure	0	5 (0.3)
Alanine aminotransferase increased	0	1 (0.1)
Anaemia	0	1 (0.1)
Atypical pneumonia	0	1 (0.1)
Colon adenoma	0	1 (0.1)
Craniocerebral injury	0	1 (0.1)
Eye injury	0	1 (0.1)
Fibrin D dimer increased	0	1 (0.1)
Hand fracture	0	1 (0.1)
Hypoxia	0	2 (0.1)
Interstitial lung disease	0	2 (0.1)
Pneumonitis	0	5 (0.3)
Pulmonary embolism	0	2 (0.1)

Table 18. Summary of Treatment-Emergent Serious Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671002 and C4671005)

Number of Participants Evaluable for AEs	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1578)	Placebo (N=1581)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Rectal haemorrhage	0	1 (0.1)
Respiratory failure	0	1 (0.1)
Road traffic accident	0	1 (0.1)
Wrist fracture	0	1 (0.1)

Participants are only counted once per treatment per event.
Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.1 coding dictionary applied.
C4671005 participants enrolled at sites 1274 and 1470 (including those switched to 1276), and C4671002 participants enrolled at sites 1281 and 1488 (including those switched to 1282) are excluded.

6.2.1.3. Deaths

There were 16 deaths among participants in the Integrated Safety Pool, all of which occurred in the placebo group. Of these, 15 were unvaccinated participants from Study EPIC-HR who were at high risk of progressing to severe disease and 1 was a vaccinated participant from Study EPIC-SR who had multiple risk factors for COVID-19. Of the 16 deaths, 14 occurred during the active safety collection period (up to Day 34) and were related to the disease under study. The remaining 2 deaths occurred during the long-term follow-up period (cause of death was related to COVID-19 for 1 participant [Day 67] and for the other participant was sepsis with underlying relapsed acute myeloid leukemia [Day 96]).

No deaths occurred in the PAXLOVID group at the time of data cut-off for the 2 studies.

6.2.1.4. Adverse Events Leading to Discontinuation of Study Intervention

In the Integrated Safety Pool, the proportion of participants who discontinued from study intervention due to AEs was similar between the PAXLOVID treatment group (2.0%) and the placebo treatment group (3.2%).

All-causality TEAEs that led to discontinuation of study intervention in more than 1 participant in the PAXLOVID treatment group were Nausea (6 participants), Vomiting (5 participants), Creatinine renal clearance decreased (4 participants), Dysgeusia (4 participants), Diarrhoea (3 participants), Glomerular filtration rate decreased (2 participants), White blood cell count decreased (2 participants), and Dizziness (2 participants).

6.2.1.5. Adverse Events Considered to be Adverse Drug Reactions

Based on the current PAXLOVID safety data, all AEs underwent internal clinical and safety review to apply medical judgement in determining ADRs likely associated with PAXLOVID.

For the purposes of labeling, the data sets used to determine ADR frequencies for PAXLOVID were the Integrated Safety Pool (Study EPIC-HR and Study EPIC-SR) and Study EPIC-PEP.

- The Integrated Safety Pool data set consisted of 1578 participants who were treated with PAXLOVID and 1581 participants who received placebo.
- The Study EPIC-PEP data set consisted of 1823 participants who were treated with PAXLOVID and 898 participants who received placebo.

The ADR is coded based on MedDRA, Version 24.1, and the ADR frequencies are categorized as per the CIOMS III/V convention[63] as detailed below:

- Very common ≥1/10 (≥10%)
- Common ≥1/100 and <1/10 (≥1% and <10%)
- Uncommon ≥1/1000 and <1/100 (≥0.1% and <1%)
- Rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%)
- Very rare <1/10,000 (<0.01%)
- Frequency not known (cannot be estimated from the available data)

The safety data presented in the ADR table (Table 19) is based on 3401 participants who received PAXLOVID and 2479 participants who received placebo in both the Integrated Safety Pool (Studies EPIC-HR and EPIC-SR) and Study EPIC-PEP (inclusive of participants who received 5- and 10-day treatment).

Table 19. Adverse Drug Reactions[a] in Participants Receiving PAXLOVID Over Duration of 5- or 10-Day Treatment (Protocol C4671005 and C4671002, and Protocol C4671006)

System Organ Class	ADR Term	Frequency n/N (%)		Category
		PAXLOVID	Placebo	
Nervous system disorders	Dysgeusia	194/3401 (5.7%)	9/2479 (0.4%)	Common
	Headache[b]	50/3401 (1.5%)	48/2479 (1.9%)	Common
Gastrointestinal disorders	Diarrhoea	98/3401 (2.9%)	47/2479 (1.9%)	Common
	Vomiting[b]	32/3401 (0.9%)	23/2479 (0.9%)	Uncommon

a. Occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group and/or likely associated with PAXLOVID based on available data and causality assessment
b. Existing ADRs included in the CDS and supported by post-marketing surveillance.

Based on ADR calculations Headache and Vomiting do not meet the criteria of 'occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group'. However, based on available data and causality assessment, the sponsor has determined that these 2 AEs should remain ADRs.

6.2.2. Safety In Special Groups and Situations

This section summarizes the safety of PAXLOVID in other special patient populations, in addition to those described previously and findings from the analyses of special safety topics, clinical laboratory values, vital signs and ECG data.

Geriatric Participants	In the Integrated Safety Pool, 324 participants were ≥65 years of age. The number of participants ≥75 years old was relatively small (N=80) and so inferences regarding safety in this subgroup are limited. More participants ≥65 years of age reported a TEAE compared to participants <65 years of age: 42.4% vs 20.1% in the PAXLOVID group and 37.1% vs 22.7% in the placebo group, respectively. In general, TEAEs reported in the participants 65 years of age and older were similar to those reported in participants <65 years of age. Creatinine renal clearance decreased (9.1%) and Fibrin D dimer increased (7.3%) were the most frequently reported TEAEs in PAXLOVID treated participants ≥65 years of age and were reported less frequently in participants <65 years of age (0.3% and 1.1%, respectively). Similarly, in the placebo group, both TEAEs were observed at higher frequency in participants ≥65 years of age. Overall safety conclusions were similar among geriatric participants compared to younger participants.
Adult Household Contacts of an Individual with Symptomatic COVID-19 (Study EPIC-PEP)	Treatment with the 5-day and 10-day regimens of PAXLOVID was safe and well tolerated. • The incidence of all-causality TEAEs was low and generally similar across treatment groups. Most all-causality TEAEs in all treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. No participants in any treatment group experienced an AE resulting in death. • No participants discontinued study due to an AE. The incidence of discontinuation of study intervention due to an AE was low and generally similar across the treatment groups.

	• Overall, the incidence of participants with hemodynamic, inflammatory, or thyroid-related adverse events of special interest (AESIs) was low and comparable between treatment groups. • Treatment with the PAXLOVID 5-day and 10-day regimens was not associated with clinically meaningful changes in laboratory values or vital signs.
Renally Impaired Participants	The safety profile in patients with moderate renal impairment is sufficiently characterized and any potential risks are appropriately mitigated through the dosing recommendations (34 participants in Study EPIC-HR with moderate renal impairment and 2 participants with severe renal impairment). In Phase 1 Study 1011, single oral administration of nirmatrelvir (100 mg) in combination with ritonavir (100 mg) had an acceptable safety and tolerability profile in adult participants with normal and impaired (mild, moderate, and severe) renal function. 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. For further details see Section 3.5.1.
Hepatically impaired Participants	No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in participants with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment. In Phase 1 Study 1010, PAXLOVID had an acceptable safety and tolerability profile in adult participants with normal hepatic function as well as those with moderate hepatic impairment. No significant laboratory trends or clinically relevant changes in vital signs or ECG parameters were observed in the study after single dose of nirmatrelvir, pharmacokinetically enhanced by ritonavir. For further details see Section 3.5.2.
Topics of Special Interest	Pre-specified AESIs including hemodynamic events, inflammatory events, and thyroid-related events were examined as part of routine safety data review procedures throughout Studies EPIC-HR, EPIC-SR, and EPIC-PEP, and as part of signal detection processes. All AESIs were reported as an AE or SAE as described in the individual study protocols. These safety topics were derived from review of the nonclinical and clinical experience with PAXLOVID. Hypersensitivity was identified as an ADR during post-marketing experience and was considered an AESI, though not pre-specified in the individual study protocols.
	<u>Hemodynamic Events</u> The incidence of participants with hemodynamic all-causality TEAEs was comparable between treatment groups. Hypertension occurred at a low but numerically higher frequency (≥5 participant difference) in the PAXLOVID group (8 participants [0.5%]) compared with the placebo group (4 participants [0.3%]). Overall, there were no clinically meaningful differences in the changes in vital sign parameters over time between the PAXLOVID group and the placebo group.

	Inflammatory Events The incidence of participants with inflammatory all-causality TEAEs was comparable between treatment groups, except for Fibrin D dimer increased, which occurred at a greater frequency (≥5 participant difference) in the placebo group (36 participants [2.3%]) compared with the PAXLOVID group (28 participants [1.8%]) and Activated partial thromboplastin time prolonged which occurred at a greater frequency (≥5 participant difference) in the placebo group (18 participants [1.1%]) compared with the PAXLOVID group (12 participants [0.8%]). Thyroid-related Events The incidence of participants with thyroid-related all-causality TEAEs was comparable between treatment groups (0.6% in the PAXLOVID group and 0.8% in the placebo group). Hypersensitivity Events The incidence of participants with hypersensitivity all-causality TEAEs (Hypersensitivity SMQ narrow scope) was higher in the placebo group (10 participants [0.6%]) compared with the PAXLOVID group (4 participants [0.3%]).
Pregnancy	Based on findings from animal studies, there were no nirmatrelvir-related severe manifestations of developmental toxicity (malformations and embryo-fetal lethality) at the highest dose tested in rats and rabbits. There were no nirmatrelvir-related adverse effects on pre- and post-natal development up to the highest dose tested in rats. Across the PAXLOVID clinical studies there were 7 cases of Maternal exposure during pregnancy – in 4 of the 7 cases, female study participants received placebo, in 3 of the 7 cases the pregnancies occurred in female partners of male study participants receiving PAXLOVID. There were no associated AEs in any of the 3 cases. As of 31 December 2022, the outcome of the pregnancies in all 3 cases was unknown. A cumulative search of post-marketing AE reports for cases reporting pregnancy or lactation through 31 December 2022 identified a total of 98 cases of Exposure during pregnancy and 14 cases involving lactation. Of the 98 cases of Exposure during pregnancy, the trimester of exposure was unknown in 19 cases. In 13, 35, and 31 cases, exposure occurred during the first, second, and third trimester of pregnancy, respectively. Infant outcome was reported in 8 cases: normal in 4 babies, 1 baby was born prematurely at 29+1 weeks and was hospitalized in the neonatal intensive care unit due to prematurity of birth (no abnormalities reported), spontaneous abortion was reported 4 days

	after the end of Paxlovid course in 1 case, 1 case reported neonatal respiratory failure (APGAR Score was 1, 8, 9, no other information on infant outcome provided) and congenital anomalies of brachial cyst and anal fistula were reported in an infant exposed during 7th month of pregnancy. A total of 14 cases involved lactation (Suppressed lactation [3 cases]; Lactation disorder [1 case] and Exposure via breastmilk [10 cases]). Based on review of available pregnancy and lactation data, no update to the label is considered at the current time.
Potential Drug Abuse, or Withdrawal	PAXLOVID treatment does not have the characteristics for being abused.
Clinical Laboratory Abnormalities, Vitals and ECG	In the Integrated Safety Pool, no clinically meaningful differences were observed between the PAXLOVID and placebo groups with respect to hematology and clinical chemistry laboratory test results. No clinically meaningful findings in vital sign were observed in the Integrated Safety Pool. The assessments and observations were comparable between treatment groups. Electrocardiogram (ECG) data were collected in the sentinel cohorts of Studies EPIC-SR and EPIC-HR. Based on the external data monitoring committee and FDA assessment of ECG data collected from the sentinel cohort of Study EPIC-HR, ECG collections were stopped.

6.3. Post-Marketing Safety

Exposure

It is estimated that 11,646,361 patients (8,595,340 in the US and 3,051,021 outside the US) have been exposed worldwide cumulatively from the first EUA in the US in December 2021 through 31 December 2022.

Post-marketing Safety Surveillance

The reported post-marketing AEs are consistent with safety data from the Phase 2/3 clinical studies (EPIC-HR+EPIC-SR and EPIC-PEP) and ADRs included in the product information.

Since the NDA submission the following label updates have been made or are proposed based on post-marketing safety surveillance:

- Anaphylaxis has been added to the sponsor's Core Data Sheet Section 4.8, Undesirable effects, as an ADR identified post-marketing (CDS version 6, effective date 22 August 2022). The sponsor proposes to add anaphylaxis to the USPI Section 6.2, Post-marketing Experience.

- Hypersensitivity Warning and Precaution has been added to the sponsor's Core Data Sheet Section 4.4 Special warnings and precautions for use. The sponsor proposes to update the Warning and Precaution in the USPI Section 5, Warnings and Precautions.

- Hypertension has been added to the sponsor's Core Data Sheet Section 4.8, Undesirable effects, as an ADR identified post-marketing. The sponsor proposes to add Hypertension to the USPI Section 6.2, Post-marketing Experience.

6.4. Post-Marketing Pharmacovigilance and Risk Mitigation

Ongoing and comprehensive pharmacovigilance activities, including pharmacoepidemiology surveillance of real-world use, support the safety conclusions of the sponsor's clinical program (Table 24). In addition, these pharmacovigilance activities support the sponsor's efforts to continuing to further characterize the safety profile of PAXLOVID in special patient populations such as pregnant patients, and patients with renal and/or hepatic impairment.

6.4.1. Drug-Drug Interactions

The sponsor acknowledges there is a risk of drug-drug interactions (DDIs) associated with the concomitant administration of PAXLOVID. DDIs due to low-dose ritonavir's inhibition of CYP3A4 is a well-known and characterized risk for ritonavir. An important distinguishing factor for PAXLOVID as compared with other low-dose ritonavir containing products is the short duration of use (5 days) versus chronic use in an HIV setting. This short-duration administration of PAXLOVID is an inherent risk mitigation factor for the risk of DDIs.

6.4.1.1. Review of Drug Interaction Post-Authorization Safety Data in the US

The sponsor's ongoing pharmacovigilance activities have supported the collection and assessment of reported cases of drug interactions. As of 31 December 2022, 22,140 US cases were received for PAXLOVID and included in the sponsor's Global Safety Database. Of these cases, there were 427 cases reporting drug interactions with contraindicated drugs or other interacting drugs that can be used with caution (as per section 7 of the Fact Sheet), representing 1.9% of all PAXLOVID post-authorization reports from the US and a reporting rate of 0.005%, based on an estimated US exposure of 8,595,340 patients (Table 20).

Table 20. Summary of Post-Authorization Cases Involving Contraindicated and Other Interacting Drugs With at Least 1 PT Suggestive of a Drug Interaction with PAXLOVID (n=427)[a]

	Overall	Contains at Least 1 Contraindicated Drug[b]	Contains at Least 1 Drug That Can Be Used with Caution[c]
Total number of Cases[d]	427[e]	273	238
Serious	83	30	67
Fatal	2	1[f]	2[f]
Hospitalization[g]	44	12	39
Nonserious	344	243	171

a. Search criteria for drug interactions: MedDRA v. 25.1 PTs Contraindicated product administered, Contraindicated product prescribed, Drug interaction, Inhibitory drug interaction, Labelled drug-drug interaction issue, Labelled drug-drug interaction medication error, Potentiating drug interaction
b: Per section 4 Contraindications of the EUA Fact Sheet.
c: Per section 7 Drug Interactions of the EUA Fact Sheet.
d: Some cases involve both contraindicated drugs and drugs that can be used with caution.
e: Events were coded to the following PTs (in some cases the reported drug interactions were coded to more than one PT): Contraindicated product administered (251), Drug interaction (128), Labelled drug-drug interaction medication error (39), Contraindicated product prescribed (28), Labelled drug-drug interaction issue (2), Inhibitory drug interaction, Potentiating drug interaction (1 each).

f: 1 case reported both a contraindicated drug and drugs that can be used with caution.
g: Hospitalization includes the cases with a fatal outcome.
MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

Most of the cases were non-serious (80.6%). Of the serious cases, 44 reported hospitalizations, 2 of which reported fatal outcome. Of note, the outcome of most cases was not necessarily due to the drug-interaction, but due to multiple confounding factors, including underlying comorbidities, concomitant medications, and COVID-19 infection, or undetermined due to insufficient information. Similarly, the 2 cases that reported fatal outcome had significant co-morbidities that contributed to their poor outcome in addition to the COVID-19 infection. The first case concerned an 86-year-old male patient. Medical history included diabetes mellitus, heart disease (unspecified), arrhythmia (unspecified), right sided heart failure pulmonary fibrosis, pulmonary hypertension, early liver disease, hypothyroidism, and anemia. The patient was taking dronedarone, which is contraindicated for use with PAXLOVID; concomitant medications included apixaban and atorvastatin, which are listed as interacting drugs (not contraindicated) in the PAXLOVID Fact Sheet. PAXLOVID therapy was discontinued after 3 days, and the patient died 5 days later. The cause of death was reported as COVID-19. The second case concerned a 59-year-old female patient. Medical history included alpha-1 antitrypsin deficiency, chronic respiratory failure, diabetes mellitus, hypertension, and hyperlipidemia. The patient experienced a reported drug interaction between PAXLOVID and nifedipine; atorvastatin was reported as a co-suspect drug. The patient had waited 10 days before starting prescribed PAXLOVID therapy, and therapy was discontinued after 2 days. The cause of death was reported as cardiac arrest following multiple events and interventions.

Overall, the adverse events associated with reports of drug interaction were consistent with the known safety profile of PAXLOVID (ie, listed ADRs or underlying COVID-19 infection). While no new safety information was identified, the sponsor will continue to monitor the risk of drug interactions as a component of routine pharmacovigilance activities.

6.4.1.2. Risk Mitigation Activities for DDIs Implemented and Ongoing under EUA

Under the EUA, in partnership with the Agency, the sponsor has implemented several risk mitigation tools and communications to amplify the awareness amongst healthcare providers of this important drug interaction and support the safe use of PAXLOVID. These risk mitigation activities include:

- Dissemination of two Dear Healthcare Provider Letters,
- A Drug Interaction Checker, accessible on the product website, which can be easily reached via a QR code on the product packaging.
- A Drug Interaction Resource describing potentially significant drug interactions, including contraindicated drugs on the Pfizer Medical Portal.

Outside of the sponsor's outreach, several risk mitigation tools are available to support appropriate PAXLOVID use:

- The Agency maintains and makes available the PAXLOVID Patient Eligibility Screening Checklist Tool, available from the FDA's website, as another resource for healthcare providers.
- The University of Liverpool maintains an extensive drug interaction checker (available by website or smartphone application) that is well recognized, user friendly, and utilized by health care providers globally.
- The National Institutes of Health maintains a website that informs clinicians of clinically relevant drug interactions and use of medications without clinically relevant interactions.

6.4.1.3. Risk Mitigation Activities for DDIs Planned under NDA

The sponsor ensures that the existing risk mitigation activities that have been implemented under EUA will continue to remain in place under NDA.

Under NDA, the sponsor proposes a comprehensive risk mitigation plan (Table 21), that will ensure further amplification of awareness for the risk of significant DDIs with PAXLOVID, while avoiding the unintended consequence of prescriber hesitation which will result in appropriate patients not receiving access to a beneficial treatment option.

A key component of the proposed risk mitigation plan is to disseminate another DHCP letter, which will ensure timely communication of the risk. The sponsor is developing Continuing Education (CE) programs provided by accredited CE providers and associated with Continuing Medical Education (CME) credits that will incentivize healthcare provider (HCP)

knowledge uptake. Furthermore, the sponsor proposes the inclusion of an Alert Box on the product packaging and FDA approved patient labeling to appropriately mitigate the risk of DDIs across the spectrum of the medication use process.

Table 21. Proposed Risk Mitigation Plan

Risk Mitigation ***Status***	Category of Risk Mitigation	Target Audience	Key Messages
Dissemination of an additional DHCP Letter *Proposed*	Inform	Prescribers Dispensers	• Provide reference to decision support tools to aid prescribing and dispensing (eg, CDC website for COVID-19 Treatments and Medications; National Institutes of Health (NIH) COVID-19 Treatment Guidelines; or EPIC Research, Pfizer DDI checker, Prescribing checklist) • Provide summary of available post-authorization data regarding risk of DDIs including most frequently prescribed CYP3A4 drugs
Continuing education framework provided to accredited CE providers *Ongoing*	Inform	Large healthcare provider continuing education providers, including but not limited to Medscape, Web MD, DIA, and PowerPak CE, to provide education and incentivize uptake through CE credits.	• Importance of DDI education o Assessing patients for potential DDIs prior to prescribing and dispensing o Provide reference to decision support tools to aid prescribing and dispensing (e.g., CDC website for COVID-19 Treatments and Medications; NIH COVID-19 Treatment Guidelines; or EPIC Research, Pfizer DDI checker, Prescribing Checklist) o Provide summary of most frequently prescribed CYP3A4 drugs
Journal information pieces Information to be disseminated at scientific meetings Healthcare Provider Fact Sheet *Proposed*	Inform	Prescribers Dispensers	• Alert on risk of DDIs • Provide reference to decision support tools to aid prescribing and dispensing (eg, CDC website for COVID-19 Treatments and Medications; NIH COVID-19 Treatment Guidelines; or EPIC Research, Pfizer DDI checker, Prescribing checklist)

Table 21. Proposed Risk Mitigation Plan

Risk Mitigation *Status*	Category of Risk Mitigation	Target Audience	Key Messages
Publication on drug interactions with PAXLOVID for most prescribed US drugs *Proposed*	Inform	Prescribers Dispensers	• Summary of risk of DDI and PAXLOVID
Prescribing Checklist *Proposed*	Prescribing Tool	Prescribers	• Decision support for prescribing including: Medical History Concomitant medication check • Patient counseling support for certain identified DDIs • Links for access to decision support tools and additional resources
Prescribing awareness poster *Proposed*	Inform	Prescribers	• Alert on risk of DDIs • How to access support tools
FDA Approved Patient Labeling *Currently Proposed in NDA Submission*	Inform	Patients	• Risk of DDIs; importance that prescribers and dispensers are aware of all concomitant medications • Other information as agreed upon with the Agency
Packaging update: Addition of Alert Box *Proposed*	Inform	Prescribers Dispensers Patients	• A red alert box to be included on the principal display panel of the carton labeling which states: "ALERT: Find out about medicines that should NOT be taken with Paxlovid"

7. REAL WORLD EVIDENCE

The aforementioned EPIC trial results are supported by real-world data that extend the evidence on clinical effectiveness of PAXLOVID to the Omicron-predominant period and to the vaccinated patient population at high risk for progression to severe COVID-19.

Several real-world studies conducted in Israel, Hong Kong, and the US demonstrate that PAXLOVID is highly effective in reducing the risk of hospitalization or death during time periods predominated by multiple Omicron subvariants, including BA.1, BA.2, and BA.4/5.[21-26,64-68] The most recent real-world estimates, which have been generated from the US during periods of Omicron BA.2 and BA.4/5 predominance, indicate effectiveness (ie, relative risk reductions) ranging from approximately 50% to 80% against hospitalization or death,[21,23,26] with similar effectiveness across vaccination status and other clinical characteristics including age group, and immunocompromised status.[23] A summary of the real-world evidence from the US for the general population is provided in Table 22. Six real-world studies conducted in the US are described below, ordered chronologically according to study period end date.

Bajema et al.[22] (non-peer reviewed preprint) reported effectiveness of PAXLOVID against the composite endpoint of all-cause hospitalization or death within 30 days after assigned index date (see below) among US veterans aged 18 years and older. The authors also evaluated intensive care unit (ICU) admission and mechanical ventilation occurring during hospitalization as secondary endpoints. This retrospective target trial emulation study using the Veterans Health Administration (VHA) COVID-19 Shared Data Resource (CSDR), which contains patient-level COVID-19-related information on VHA enrollees, included patients with a first positive SARS-CoV-2 test in CSDR between 01 January 2022 and 28 February 2022, a period predominated by the Omicron BA.1 subvariant.

To control for bias, two matching steps were used to achieve balance of covariates between comparator groups and reduce confounding. Eligible PAXLOVID-treated patients were first exact-matched to eligible untreated patients as of their assigned index date, defined as the treatment date (if treated) or the date that was the same number of days after the date of first positive SARS-CoV-2 test as the treatment date of the matched treated patients, on three factors: National Institutes of Health (NIH) tier of prioritization for anti-SARS-CoV-2 therapies, VA Integrated Service Network, and calendar time. An additional propensity score matching step with replacement was performed in a 1:k variable ratio, where k varied based on the number of propensity score ties. The propensity score logistic regression model predicting treatment included demographic, geographic, healthcare utilization, and clinical factors that were selected a priori.

Up to 4 untreated patients were matched to each treated patient. Unadjusted risk rates, risk differences, and risk ratios were calculated. All analyses were importance-weighted to account for variable-ratio matching. The final analysis population included 1,587 PAXLOVID-treated patients (and 1,587 weighted matched controls) with a median age of 65 years and 89% males, 71% of whom were vaccinated. Compared to no treatment, effectiveness of PAXLOVID treatment within 10 days of diagnosis against the primary

composite outcome (hospitalization or death), was 47% (95% CI: 28% to 61%) and was similar across vaccination status (52% [95% CI: 27% to 68%] for primary or booster vaccinated, and 39% [95% CI: 3% to 62%] for unvaccinated). Against the individual outcomes of (ICU) admission and mechanical ventilation (secondary endpoints), effectiveness was 56% (95% CI: 14% to 78%) and 49% (95% CI: -75% to 85%), respectively, compared to no treatment. Of note, this study evaluated PAXLOVID treatment within 10 days of diagnosis.

Ganatra et al.[25] reported effectiveness of PAXLOVID against all-cause, hospitalization within 30 days after outpatient diagnosis (if untreated) or initiation of treatment (if treated) among vaccinated US adults aged 18 years and older as a secondary endpoint. This retrospective cohort study using the TriNetX Analytics Network database, which contains data on over 88 million patients from 59 healthcare organizations, included patients developing COVID-19 between 01 December 2021 and 18 April 2022, a period predominated by Omicron subvariants BA.1 and BA.2. To control for bias, 1:1 propensity score matching based on patient demographics, comorbidities, medications, and laboratory test results was utilized to balance baseline differences in the patient cohorts. After propensity score matching, odds ratios were calculated. The final analysis population included 2,260 adults (1,130 treated and 1,130 untreated), all of whom were vaccinated. Information on history of prior SARS-CoV-2 infection was not reported. Against the individual outcome of all-cause hospitalization (secondary endpoint), effectiveness was 60% (95% CI: 9% to 80%).

Dryden-Peterson et al.[24] reported effectiveness of PAXLOVID against the composite endpoint of hospitalization within 14 days or death within 28 days after an outpatient diagnosis of COVID-19 among US adults aged 50 years and older. The authors also evaluated individual components of the composite primary outcome as secondary endpoints. This population-based cohort study using data from Mass General Brigham, a non-profit integrated healthcare system that cares for 1.5 million patients annually throughout Massachusetts and southern New Hampshire, included patients developing COVID-19 between 01 January and 17 July 2022, a period predominated by Omicron subvariants BA.1, BA.2, BA.2.12.1, and BA.5 in the region. To control for bias, inverse probability treatment weights were generated using a logistic model that included a priori selected factors of age, comorbidity score, vaccination status, recency of last vaccine dose, self-reported race and ethnicity, study period, and neighborhood disadvantage. Modified Poisson models using robust error variance that accounted for the weighted design were then used to calculate risk ratios. The final analysis population included 44,045 adults, 66% of whom were vaccinated and boosted. Information on history of prior SARS-CoV-2 infection was not reported. Against the primary composite endpoint (hospitalization or death), effectiveness of PAXLOVID prescription received at any time after diagnosis was 44% (95% CI: 25% to 58%) and was similar across age group, comorbidity scores, and obesity status. Effectiveness was higher for adults who had received fewer than 3 vaccine doses [81% (95% CI: 51% to 92%)] than for those with ≥3 doses [31% (95% CI: 6% to 50%)], and protection appeared higher with longer time since last vaccine dose [55% (95% CI: 36% to 68%) when last vaccine was >20 weeks ago]. Against the secondary endpoints, effectiveness was 40% (95% CI: 19% to 56%) for hospitalization and 71% (95% CI: 29% to 88%) for death.

Aggarwal et al.,[21] reported effectiveness of PAXLOVID against all-cause hospitalization within 28 days of a positive SARS-CoV-2 test (primary endpoint), based on the observed or imputed test date. COVID-19-related 28-day hospitalization and 28-day all-cause mortality were evaluated as secondary endpoints. This retrospective cohort study using electronic health records of University of Colorado Health, the largest health system in Colorado with 13 hospitals and numerous ambulatory sites and affiliated pharmacies around the state, included patients diagnosed with SARS-CoV-2 infection between 26 March and 25 August 2022, a period predominated by Omicron subvariants BA.2 and BA.4/5. Diagnosis was identified using records for SARS-CoV-2 positive test date or PAXLOVID medication order date if a test result was unavailable. To control for bias, nearest neighbor propensity matching with logistic regression was performed. The propensity score logistic regression model predicting treatment included age, sex, race, ethnicity, insurance status, immunocompromised status, obesity status, number of comorbid conditions (other than immunocompromised status and obesity), number of COVID-19 vaccinations, and calendar week of positive test date. Any remaining imbalance was adjusted for in outcome models, and final models additionally adjusted for Omicron subvariant. The final analysis population included 16,529 adults (1.31:1 treated to untreated), of whom 59% were vaccinated with ≥3 doses. Information on history of prior SARS-CoV-2 infection was not reported. Against the primary endpoint of all-cause hospitalization, effectiveness of PAXLOVID prescription received any time after diagnosis was 55% (95% CI: 38% to 67%) and was not statistically different across age group, immunocompromised status, vaccination status, or Omicron subvariant. Against the secondary endpoints of COVID-19-related hospitalization and all-cause mortality, effectiveness was 60% (95% CI: 43% to 72%) and 85% (95% CI: 50% to 97%), respectively.

In a CDC Morbidity and Mortality Weekly Report (MMWR), Shah et al.[23] reported effectiveness of PAXLOVID against overnight Covid-19 hospitalization (primary endpoint) and against all-cause hospitalization and acute respiratory illness-associated hospitalization (secondary endpoints) within 30 days after outpatient diagnosis among US adults aged 18 years and older. This retrospective cohort study using Cosmos, a data set containing electronic health record information on over 160 million patients in US health systems covered by the healthcare software company Epic, included patients developing Covid-19 between 01 April and 31 August 2022, a period predominated by Omicron subvariants BA.2 and BA.4/5. To control for bias, multivariable Cox proportional hazards models adjusted for age, sex, race and ethnicity, social vulnerability index, number of underlying health conditions, US Census Bureau region of residence, previous infection, and Covid-19 vaccinations status (excluding the stratum of interest). The final analysis population included 693,084 adults, of whom 66% were vaccinated with ≥2 doses and 15% had a history of prior SARS-CoV-2 infection (defined as a diagnosis or positive test result more than 90 days before the current diagnosis). Against the primary endpoint of overnight Covid-19 hospitalization, effectiveness of PAXLOVID prescription within 5 days of diagnosis was 51% (95% CI: 47% to 54%) and was not statistically different across age group, vaccination status (50% effectiveness for unvaccinated, vaccinated with 2 mRNA doses, and vaccinated with ≥3 mRNA doses, respectively), immunocompromised status, and month of Covid-19 diagnosis. Overall estimates against the secondary endpoints (all-cause and acute respiratory infection-related hospitalization) were similar to those for the primary endpoint.

Lewnard et al. (non-peer reviewed preprint) reported effectiveness of PAXLOVID against the composite endpoint of hospitalization or death due to any cause within 30 days of a positive SARS-CoV-2 test result among individuals aged 12 years and older.[26] The authors also evaluated a secondary composite endpoint of intensive care unit admission, mechanical ventilation, or death within 60 days of the index positive SARS-CoV-2 test result as a measure of progression to more severe disease. This retrospective cohort study using data within Kaiser Permanente Southern California, an integrated care health system with 4.7 million members (~19% of the southern California population), included patients developing Covid-19 between 08 April and 07 October 2022, a period predominated by Omicron subvariants BA.2 and BA.4/5. Of note, this study had data about date of symptom onset available. To control for bias, regression strata were created that matched on week of SARS-CoV-2 testing, age, sex, clinical status (measured according to 2 criteria: 1) receipt of any clinical care in association with testing; and 2) days from symptom onset or absence of acute symptoms), healthcare utilization in the prior year, Covid-19 vaccine doses received, presence of comorbidities, and body mass index category. Multivariable Cox proportional hazards models with differing baseline hazards across all combinations of the regression strata additionally adjusted for race/ethnicity, cigarette smoking, documentation of prior SARS-CoV-2 infection, neighborhood deprivation, and receipt of non-Covid vaccines (as an additional measure of healthcare-seeking behavior). The final analysis population included 133,426 patients (7,274 treated and 126,152 untreated), of whom 86% were vaccinated with ≥2 doses, 61% were vaccinated with ≥3 doses, and 4% had documentation of prior SARS-CoV-2 infection. Against the primary composite outcome (hospitalization or death), effectiveness of PAXLOVID treatment was higher when treatment was received within 5 days of symptom onset (80% [95% CI: 34% to 94%]) than when treatment was received at any time after diagnosis (54% [95% CI: 7% to 77%]) (Table 22 and Table 23).

Effectiveness within 5 days of symptom onset increased (from 80%) to 90% (95% CI: 50% to 98%) when patients were dispensed treatment on the same day as testing. Subgroup results for the primary outcome among vaccinated patients were similar. For treatment received within 5 days of symptom onset, effectiveness was 83% (95% CI: 30% to 96%) and 92% (95% CI: 52% to 99%) among patients vaccinated with ≥2, and ≥3 doses, respectively. For treatment received at any time after diagnosis (regardless of symptom timing), effectiveness was 55% (95% CI: 7% to 79%) and 67% (95% CI: 24% to 85%) among patients vaccinated with ≥2, and ≥3 doses, respectively. Against the secondary composite endpoint (ICU admission, mechanical ventilation, or death), effectiveness was 89% (95% CI: -25% to 99%) for treatment received within 5 days of symptom onset, and 84% (95% CI: 19% to 97%) for treatment received at any time after diagnosis.

In summary, the 6 real-world evidence studies described above provide supportive evidence on the high effectiveness of PAXLOVID against hospitalization or death in the US. All 6 US studies were conducted after the emergence and global predominance of the Omicron variant, in a setting of high prevalence of prior immunity acquired from vaccination, natural infection, or both. Estimates of PAXLOVID effectiveness against hospitalization or death that evaluated treatment either within 5 days, or any time, after the diagnosis date (rather than symptom onset date) ranged from approximately 45% to 60% and were lower than estimates that anchored treatment timing to symptom onset date, of approximately 80%. All 6 studies

found that PAXLOVID was effective against hospitalization or death among vaccinated patients, and one study showed increased clinical benefit with earlier treatment.

Overall, the available real-world data on PAXLOVID demonstrates that the antiviral therapeutic is highly effective in reducing the risk of hospitalization or death from COVID-19 during the Omicron-predominant period. This benefit extends to vaccinated and boosted patients at high risk for progression to severe COVID-19 and eligible for treatment. Given that COVID-19 still causes 4000–5000 hospital admissions and 500–600 deaths each day in the US as of January 2023,[29] the vast majority of which occur in high-risk individuals who are eligible for PAXLOVID,[69] many of these hospitalizations and deaths remain preventable with prompt treatment with PAXLOVID.

Table 22. Key US Studies on Real-world Effectiveness of PAXLOVID Against Omicron and Among Vaccinated Individuals Among the General Population

Study Characteristic	Ganatra et al. CID[25] (No funding)	Dryden-Peterson et al. Ann Intern Med[24] (NIH funded)	Aggarwal et al. Lancet Infect Dis[21] (NIH funded)	Shah et al. CDC MMWR[23] (CDC funded)	Lewnard et al. medRxiv[26] (CDC and NIH funded)
Endpoint	Hospitalization, death (30-day)	Hospitalization or death (14 & 28 days, respectively)	Hospitalization (28-day)	Hospitalization (30-day)	Hospitalization or death (30-day)
Index period (date of diagnosis or positive test)	01 Dec 2021 – 18 Apr 2022 (BA.1 & BA.2)	01 Jan – 17 Jul 2022 (BA.1, BA.2, & BA.4/5)	26 Mar – 25 Aug 2022 (BA.2 & BA.4/5)	01 Apr – 31 Aug 2022 (BA.2 & BA.4/5)	08 Apr – 07 Oct 2022 (BA.2 & BA.4/5)
Data source	TriNetX (>88M)	Mass General Brigham (1.5M)	Univ. of CO Health (largest health system in CO)	EPIC Cosmos (>160M)	Kaiser Permanente S. Cal. (4.7M)
Population and analysis sample size	≥18 years n = 2260 (matched 1:1)	≥50 years n = 44,045	≥18 years n = 16,529 (matched 1.31:1)	≥18 years n = 693,084	≥12 years n = 133,426 (matched 1:n)
Percent Vaccinated (among analysis sample)	100% "vaccinated"	66% ≥3 doses	59% ≥3 doses	66% ≥2 mRNA doses	86% ≥2 doses
Control for bias	Propensity Matching	Inverse Probability Tx Weights	Propensity Matching & Multivariable Logistic models	Multivariable Cox PH models	Matching & Multivariable Cox PH models
Effectiveness† (95% CI) based on time of diagnosis or test	Tx w/in 5d of diagnosis: 60% (9, 80)	Tx any time after positive test: 44% (25, 58) <3 doses: 81% (51, 92) ≥3 doses: 31% (6, 50)	Tx any time after diagnosis: 55% (38, 67) 1-2 doses: 60% (21, 80) ≥3 doses: 53% (26, 71)	Rx w/in 5d of diagnosis: 51% (47, 54) 2 mRNA doses: 50% (42, 58) ≥3 mRNA doses: 50% (45, 55)	Tx any time after positive test: 54% (7, 77) ≥2 doses: 55% (7, 79) ≥3 doses: 67% (24, 85)
Effectiveness† (95%CI) based on time of symptom onset	**NA**	**NA**	**NA**	**NA**	Tx w/in 5d of *symptom onset*: 80% (34, 94) ≥2 doses: 83% (30, 96) ≥3 doses: 92% (52, 99)

† [Measured as 1 – relative risk]

CO=[Colorado]; ED=[emergency department]; d=day; NA=not applicable; PH=[proportional hazards]; Rx=prescription; Tx=treatment; w/in=within;

Table 23. Effectiveness of PAXLOVID in Preventing Progression to All-Cause Hospital Admission or Death Within 30 Days From Positive SARS-CoV-2 Test[26]

Timing of treatment dispense in relation to symptom onset	Effectiveness, % (95% CI)
All patients	
0–3 days after symptom onset	81 (34, 95)
0–5 days after symptom onset	80 (34, 94)
At any time	54 (7, 77)
Patients dispensed treatment on the same day as testing	
0–5 days after symptom onset	90 (50, 98)
At any time	78 (31, 93)
Patients vaccinated with ≥2 COVID-19 vaccine doses	
0–5 days after symptom onset	83 (30, 96)
At any time	55 (7, 79)
Patients vaccinated with ≥3 COVID-19 vaccine doses	
0–5 days after symptom onset	92 (52, 99)
At any time	67 (24, 85)

8. SPECIAL TOPICS RELATED TO DISEASE UNDERSTANDING IN CONTEXT OF PAXLOVID TREATMENT

Rebound in COVID-19 symptoms or viral RNA level:

- Incidence similar between PAXLOVID and placebo treatment groups
- Not associated with severe COVID-19 illness, including COVID-19-related hospitalization or death
- Not associated with low nirmatrelvir exposure
- Not associated with emergence of resistant viral mutations
- Subject of ongoing study and surveillance

8.1. Treatment Durability (Viral and Symptom Rebound)

Viral and symptom rebound assessment has been conducted in both EPIC-HR and EPIC-SR studies.

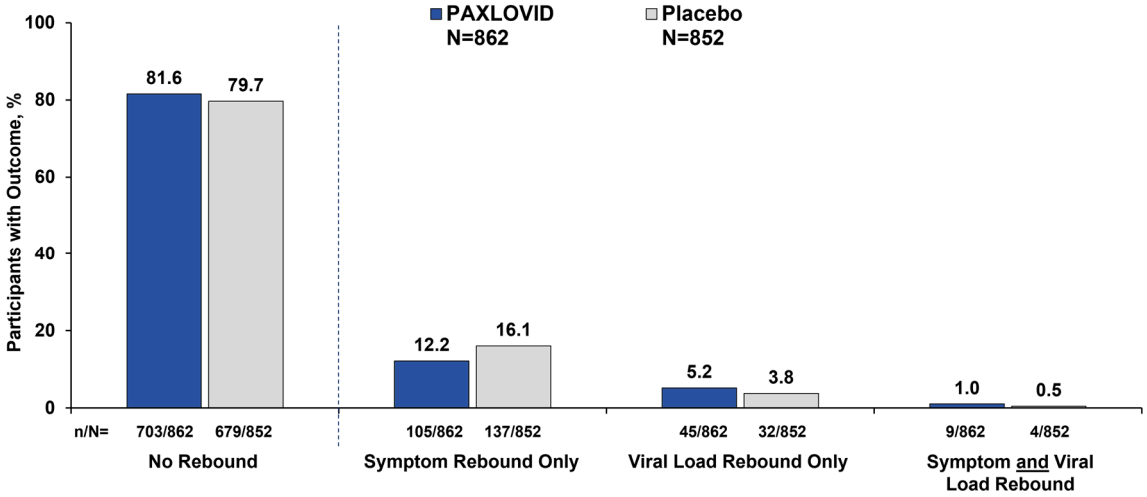
8.1.1. Viral and Symptom Rebound in EPIC-HR

The incidence of viral RNA and symptom rebound following a full 5-day course of treatment was assessed in Study EPIC-HR.

- Viral RNA rebound was defined as a recurrence of viral RNA levels $\geq$3.0 $\log_{10}$ copies per/mL by Day 10 and/or Day 14 and the increase had to be at least $\geq$0.5 $\log_{10}$ copies/mL relative to Day 5 viral RNA levels.
- Symptom rebound was defined as any improvement in COVID-19 signs and symptoms that subsequently worsened (total symptom score increased by $\geq$4).

Figure 12 illustrates the rebound recurrence in Study EPIC-HR. Viral RNA and symptom rebounds were numerically similar across treatment groups (symptom rebound only: 12.18% PAXLOVID and 16.08% placebo; viral RNA rebound only: 5.22% PAXLOVID and 3.76% placebo). Interestingly, symptom and viral RNA rebound rarely coincided (symptom *and* viral rebound 1.04% PAXLOVID and 0.47% placebo).

Figure 12. Viral RNA[a] and Symptom[b] Recurrence in Study EPIC-HR



[a] Rebound in viral load defined as: 1). if VL <LLOQ at Day 5, Day 10 or 14 VL ≥3 $\log_{10}$ copies/mL; 2). if VL ≥LLOQ at Day 5, Day 10 or 14 VL increases by ≥0.5 $\log_{10}$ copies/mL from Day 5, and the Day 10 or 14 VL has to be ≥3 $\log_{10}$ copies/mL.
[b] Symptom rebound is defined as: any improvement in COVID-19 signs/symptoms and subsequently worsened, increased by ≥4 in total symptom score.

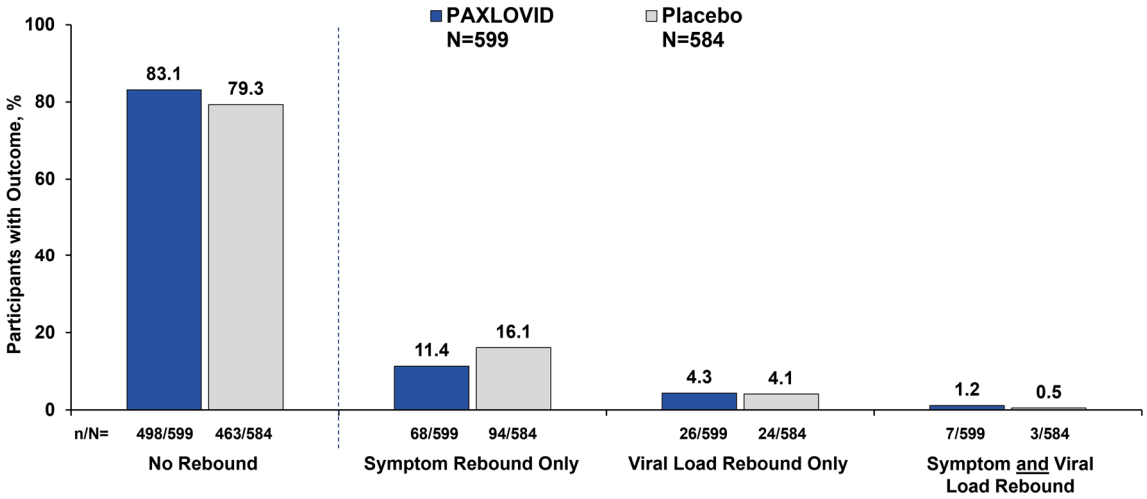
Analysis of nirmatrelvir exposure in symptom and viral RNA rebound participants showed that nirmatrelvir concentrations were comparable to the overall Study EPIC-HR population. Viral RNA and symptom rebound was not associated with recurrence of hospitalization or severe disease, or the emergence of resistant viral strains in COVID-19 rebound participants. Following rebound, samples with positive infectious titers were rare and generally associated with higher viral RNA levels (>5.0 $\log_{10}$ copies/mL).

8.1.2. Viral and Symptom Rebound in Study EPIC-SR

The incidence of viral RNA and symptom rebound was also examined in Study EPIC-SR (Figure 13). Symptom and viral RNA rebounds were numerically similar (symptom rebound: 11.35% PAXLOVID and 16.10% placebo; viral RNA rebound: 4.34% PAXLOVID and 4.11% placebo) across treatment groups and again, symptom and viral RNA rebounds rarely coincided (symptom *and* viral rebound 1.17% PAXLOVID and 0.51% placebo).

The incidence of viral RNA and symptom rebound in vaccinated high-risk participants were generally similar to the overall Study EPIC-SR population (symptom rebound only: 10.53% PAXLOVID and 16.72% placebo; viral RNA rebound only: 4.28% PAXLOVID and 3.83% placebo). Similarly, symptom and viral RNA rebounds rarely coincided (symptom and viral rebound 0.99% PAXLOVID and 1.05% placebo).

Figure 13. Viral RNA[a] and Symptom[b] Recurrence in Study EPIC-SR



[a] Rebound in viral load defined as: 1). if VL <LLOQ at Day 5, Day 10 or 14 VL ≥3 $\log_{10}$ copies/mL; 2). if VL ≥LLOQ at Day 5, Day 10 or 14 VL increases by ≥0.5 $\log_{10}$ copies/mL from Day 5, and the Day 10 or 14 VL has to be ≥3 $\log_{10}$ copies/mL.
[b] Symptom rebound is defined as: any improvement in COVID-19 signs/symptoms and subsequently worsened, increased by ≥4 in total symptom score.

8.1.2.1. Overall Conclusion on Viral Rebound from Clinical Studies

Overall, there were similar symptom or viral RNA rebound rates across PAXLOVID and placebo treatment groups and across studies, and rebounds were not associated with low nirmatrelvir exposure, the recurrence of severe disease or the emergence of resistant viral strains through Day 14.

8.2. Post-Marketing Reports on Viral Rebound

The sponsor has undertaken a cumulative search using the Global Safety Database of the post-marketing reports indicative of rebound of COVID-19 received through 31 December 2022 (MedDRA v. 25.1 search criteria: Preferred Terms; Breakthrough COVID-19, Disease recurrence, Rebound effect, Symptom recurrence; LLTs COVID-19 recurrent, COVID-19 reinfection, SARS-CoV-2 reinfection).

The review indicated that there is no safety concern associated with rebound. Most cases are nonserious (96.3%). In most cases where the outcome was reported, the events were resolved or resolving, and the overall reporting rate of rebound is low (0.1%). These data are consistent with that reported in the literature including reported untreated COVID-19 rebound rates (Section 8.3).

8.3. Literature on COVID-19 Rebound

Recent publications have demonstrated a consistently low rate of COVID-19 rebound when defined either by rapid antigen test (RAT), symptomatology or by RT-PCR.[25,28,70] Rapidly emerging data continue to highlight the low rate of rebound (despite differing definitions), lack of association with severe disease/hospitalization, and lack of association with treatment (ie, also observed at a similar rate in placebo-treated patients in Study EPIC-HR [See Section 8.1.1]; recent reports of rebound in molnupiravir treated patients).

- Deo et al reported viral rebound rates in the placebo group of the ACTIV-2 study in which daily nasal swabs were collected through study day 14, and at day 21 and 28, for quantification of SARS-CoV-2 RNA. Using a definition of viral rebound similar to the Study EPIC-HR [See Section 8.1.1], the rate of rebound in ACTIV-2 placebo cohort was 12% suggesting that Study EPIC-HR and Study EPIC-SR rebound rates are in line with reported untreated COVID-19 rebound rates.[28,62]

- A recent study highlighted that less than 1% of PAXLOVID treated individuals were hospitalized or had emergency department encounters for COVID-19 in the 5 to 15 day period after treatment.[71]

- A second study reported very low rate of symptom rebound among PAXLOVID treated individuals (4 patients; 0.8%), with symptoms being generally mild.[72]

- Wang et al reported COVID-19 rebound infection rates for both PAXLOVID and molnupiravir.[73] In this study rates of COVID-19 rebound infections were noted to be similar between the 2 drugs despite the different mechanisms of action.

- Viral RNA rebound has been described in SARS-CoV-2 natural history studies prior to the availability of oral antivirals,[74,75] suggesting viral kinetics can be bi- and multi-phasic.

The sponsor has recently submitted (June 2022) a manuscript titled 'Viral Load Rebound in Placebo and Nirmatrelvir-Ritonavir Treated COVID-19 Patients is not Associated with Recurrence of Severe Disease or Mutations' and a Letter to the Editor on this topic.[76,77]

In an NIH-sponsored case study which included 6 patients with clinical (ie, symptomatic) COVID-19 rebound after completing PAXLOVID treatment (of which 4 became RAT positive again when rebound symptoms returned), none of the patients developed severe symptoms or required additional therapy. In addition, adaptive immunity against SARS-CoV-2 appeared intact, with the authors suggesting that a more robust immune response rather than uncontrolled viral replication characterizes these clinical rebounds.[78]

8.3.1. Overall Conclusion on Viral Rebound

Based on the sponsor's review of rebound in clinical studies with PAXLOVID, and the available literature, rebound of signs or symptoms with or without a rebound in viral RNA titers occurs infrequently, does not lead to severe disease, and occurs independent of PAXLOVID treatment. Indeed, as highlighted in a recent CDC communication, a brief return of viral RNA and/or symptoms may be part of the natural history of SARS-CoV-2 infection in some persons, independent of treatment with PAXLOVID and regardless of vaccination status.[27]

9. BENEFIT/RISK ASSESSMENT IN THE CONTEXT OF PROPOSED INDICATION

In Study EPIC-HR, in non-hospitalized, unvaccinated symptomatic adult participants with COVID-19 and risk factors for progression to severe disease, a 5-day regimen of PAXLOVID initiated within 5 days of symptom onset, significantly decreased SARS-CoV-2 viral RNA concentration and improved clinical outcome as observed by a significant and clinically meaningful 85.8% reduction in COVID-19-related hospitalization or death from any cause through Day 28 when compared to participants receiving placebo (Section 4.3.1.4). The reported safety data indicates that PAXLOVID has a favorable safety profile.

An interim analysis (IA) conducted for Study EPIC-HR at ~45% of participants (1294) met pre-specified criteria for stopping the trial due to overwhelming efficacy (PAXLOVID was superior to placebo in the mITT analysis set for reduction in hospitalization for the treatment of COVID-19, and death from any cause; $p<0.0001$, the prespecified p-value per protocol to stop the trial for efficacy was $p<0.002$). Further enrolment in the study was stopped; results from this IA comprise the primary statistical interpretation for Study EPIC-HR. The effectiveness of PAXLOVID was demonstrated for participants who were at increased risk of severe COVID-19. Both the primary (mITT) and the first key secondary (mITT1) analyses showed significant treatment benefit ($p<0.0001$) in a sequential testing procedure pre-specified in the protocol. The relative reduction in COVID-19-related hospitalization or death from any cause through Day 28 was 89.1% when treatment was initiated within 3 days of symptom onset, and 84.3% when treatment was initiated within 5 days of symptom onset.

The overwhelming efficacy of PAXLOVID in Study EPIC-HR was confirmed in the LPLV analyses (2113 participants), with 89.1%, and 85.8% relative reduction in COVID-19-related hospitalization or death from any cause through Day 28 when treatment was initiated within 3 days of symptom onset ($p<0.0001$) or within 5 days of symptom onset ($p<0.0001$), respectively.

Persistent efficacy of PAXLOVID relative to placebo in a clinical setting is demonstrated by the higher proportion of participants achieving sustained COVID-19-related symptom alleviation and symptom resolution, lower COVID-19-related symptom rebound among those achieving symptom resolution, reduction in COVID-19-related hospitalization or death through Day 28 and 100% reduction in all-cause mortality through Week 24, continued reduction in viral RNA levels over time, and no indication of potential antiviral drug resistance.

There were 16 deaths among participants in the Integrated Safety Pool (Study EPIC-HR and Study EPIC-SR), all of which occurred in the placebo group. Of these, 15 were unvaccinated participants from Study EPIC-HR who were at high risk of progressing to severe disease and 1 was a vaccinated participant from Study EPIC-SR who had multiple risk factors for COVID-19 (Section 6.2.1.3).

The final reported safety data at Day 34 indicates that PAXLOVID has a favorable safety profile. The safety profile of PAXLOVID showed a consistent pattern across the Integrated Safety Pool (Study EPIC-HR + Study EPIC-SR); which included both vaccinated and unvaccinated adult participants with at least 1 factor for progressing to severe disease and unvaccinated participants without risk factors for severe disease, and

in the supportive Study EPIC-PEP (adult household contacts of an individual with symptomatic COVID-19). The 5-day regimen of PAXLOVID was safe and well-tolerated across all studies. In addition, the 10-day regimen of PAXLOVID in Study EPIC-PEP, was safe and well-tolerated. These conclusions are confirmed by the analysis of Week 12 and Week 24 data in Study EPIC-HR.

PAXLOVID maintains efficacy against the main VOC dominant during study conduct including Delta and Omicron (Section 5.1).

To date, there has been no evidence of viral resistance to PAXLOVID in treated participants. Specifically, there were no baseline M^{pro} gene or cleavage region mutations associated with treatment failure or a failed viral load response. Treatment with PAXLOVID was not associated with M^{pro} gene or cleavage region TEMs. In cases (~2-7%) where viral RNA level rebound occurred, these rebounds were not associated with PAXLOVID treatment, low nirmatrelvir exposure, COVID-19-related hospitalization or death, severe symptom relapse or treatment emergent M^{pro} gene/cleavage mutations.

Overall, appraisal of the benefit-risk for PAXLOVID is positive. Moreover, there remains an unmet medical need for an effective oral antiviral therapeutic for COVID-19.

PAXLOVID is a new oral antiviral therapeutic for non-hospitalized symptomatic patients with COVID-19 who are at increased risk of progression to severe illness. The medical need and the benefit-risk summary for the treatment of COVID-19 for both these indications are presented in Table 24.

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition		
Prevalence	Worldwide >753 million confirmed cases including 6.8 million deaths, as of February 2023.[8]	Remdesivir data in non-hospitalized individuals supports the concept that antiviral medications provide maximal benefit (reduced hospitalization and death) when used early in the disease course.[79] Emerging VOC, which may demonstrate reduced susceptibility to available mAb, and uncertainty regarding durability of vaccine protection, make it important for antiviral therapies to be available.
Clinical Manifestations	COVID-19 presentation can range from a mild to moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath to severe life-threatening symptoms resulting in pneumonia, severe acute respiratory syndrome, hypercoagulation, kidney failure and death.	
Comorbidities	Older age (>60 years), overweight (BMI >25 kg/m^2), current smoker, CKD, diabetes, immunosuppressive disease or immunosuppressive treatment, CV, or hypertension, CLD, SCD, neurodevelopmental disorders, active cancer.	
Approved available outpatient therapies for COVID-19	A trial investigating the antiviral agent remdesivir in the outpatient setting was stopped early due to feasibility; however, available data indicated that remdesivir following 3 days of IV administration demonstrated a significant 87% reduction of COVID-19 related hospitalization compared with PBO.[79] Remdesivir is currently indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg) with positive results of SARS-CoV-2 viral testing, who are: hospitalized, or not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[80]	Given the potential for SARS-CoV-2 variants to evade the immune system despite natural infection or vaccination, and limitations with remdesivir treatment, there is an urgent unmet medical need for a safe and effective oral therapeutic intervention for non-hospitalized patients with COVID-19. The antiviral would be able to reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalization, and death, in addition to lowering the strain on the healthcare system caused by SARS-CoV-2, by: - Targeting a highly conserved viral enzyme essential for replication, would provide an

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Current Treatment Options	Molnupiravir has received authorization for emergency use for patients ≥18 years for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.[81] Although molnupiravir reported an approximate 50% risk reduction of COVID-19-related hospitalization or death in its preliminary analysis,[82] the final analysis in 1433 patients with at least one risk factor for progression of COVID-19, showed 6.8% hospitalization or death in the molnupiravir group vs 9.7% in the placebo group (a 31% risk reduction).[83] Currently, molnupiravir is not authorized for use in patients <18 years of age, and not recommended for use in pregnant patients.[84] Individuals vaccinated against COVID-19 were excluded in clinical trials with remdesivir and molnupiravir.[84,85]	effective therapeutic agent against current and future SARS-CoV-2 variants. - Offering an oral antiviral agent for adults with an easy and convenient method of drug administration, taken outside of the hospital setting. - Integrated analysis demonstrates 83.5% relative risk reduction of hospitalization or death from any cause in non-hospitalized symptomatic adult participants with COVID-19 who were either vaccinated or unvaccinated, and at increased risk of progression to severe disease, when treatment was initiated within 5 days of symptom onset. This helps keep patients out of hospitals lowering the impact on the healthcare setting. - Providing safety benefits over an IV therapeutic by minimizing potential complications of IV administration and reducing IV-related medication errors.
EUA of therapeutic mAbs (bamlanivimab and etesevimab; casirivimab and imdevimab; sotrovimab; tixagevimab and cilgavimab) using either IV, IM, or SC administration.	mAb cocktails have been shown to be an effective therapy for treatment of mild to moderate COVID-19, with an acceptable safety profile. Most reported TEAEs with mAbs were generally similar to placebo. Concerns over reduced effectiveness against VOC and safety issues for the use and continued effectiveness of mAbs include the possibility of ADE, the potential for attenuation of long-term immunity, and the emergence of resistant variants under selective pressure of mAb treatment. Clinical worsening of COVID-19 after administration of mAbs has been reported	

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
	although it is not known whether these events were related to mAb use or were due to progression of COVID-19. Recently, the FDA updated the HCP Fact Sheets for bamlanivimab and etesevimab together, etesevimab alone, bebtelovimab alone and REGEN-COV based on emerging data that these treatments are unlikely to retain activity against the Omicron variant and the US Government has paused distribution. Only tixagevimab and cilgavimab (EVUSHELD, used only for pre-exposure prophylaxis) appears to retain efficacy against the Omicron variant.[15,86-88] However, recently (26 Jan 2023), the EUA for EVUSHELD was withdrawn by FDA as data show that this product is unlikely to be active against certain SARS-CoV-2 variants which are projected to be responsible for more than 90% of current infections in the US.[16] Thus, SOC is rapidly changing with mAbs.	
Benefit of PAXLOVID **Pivotal Study EPIC-HR**: An interventional efficacy and safety, Phase 2/3, double blind, placebo-controlled trial planned in ~3000 non-hospitalized symptomatic participants with COVID-19 who were at increased risk of progression to severe illness. - 2113 participants in Study EPIC-HR completed efficacy assessments through Day 28 and 3159 participants have completed follow-up safety assessments through Day 34 for the primary safety pool (Studies EPIC-HR and EPIC-SR).	Pivotal Study EPIC-HR LPLV analysis: • The primary efficacy analysis result (mITT population) demonstrated that PAXLOVID reduced COVID-19-related hospitalization or death from any cause by 89.1% compared to placebo when treatment was initiated within 3 days of symptom onset in participants with COVID-19. • The first key secondary analysis (mITT1 population) similarly showed that PAXLOVID reduced COVID-19-related hospitalization or death from any cause by 85.8% compared to	PAXLOVID was effective in reducing hospitalization and death, meeting the primary and the first key secondary efficacy endpoints. A significant reduction in viral RNA level was also seen in participants who received PAXLOVID versus PBO. Treatment with PAXLOVID significantly reduces the duration and severity of COVID-19 signs and symptoms compared with PBO. In cases (~2-7%) where viral RNA level rebound occurred (EPIC-HR), viral RNA level rebounds

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
	placebo when treatment was initiated within 5 days of symptom onset. • Results from Study EPIC-HR showed consistent risk reduction in COVID-19-related hospitalization or all-cause death across prespecified participant subgroups in the mITT1 analysis set. • The second key secondary analysis (mITT1 population) showed that PAXLOVID significantly shortened the median time to sustained alleviation of all targeted COVID-19 related symptoms through Day 28 from 15 days to 13 days. The hazard ratio for treatment with PAXLOVID versus placebo was 1.27 (95% CI: 1.134, 1.412; p<0.0001), indicating participants in the PAXLOVID group were 27.0% more likely to achieve sustained alleviation of all targeted signs and symptoms compared with placebo.	were not associated with PAXLOVID treatment, low nirmatrelvir exposure, COVID-19-related hospitalization or death, severe symptom relapse or treatment emergent M^{pro} gene/cleavage mutations. PAXLOVID is an effective antiviral agent for treatment of COVID-19.
Supportive Interim Analysis Study EPIC-SR:	In vaccinated high-risk participants, PAXLOVID treatment resulted in a non-statistically significant reduction in the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo in non-hospitalized symptomatic adult participants with COVID-19 who were at standard risk of progression to severe illness. PAXLOVID demonstrated a 57.6% relative risk reduction in vaccinated participants who had ≥1 risk factor for severe COVID-19 illness (nominal p=0.197).	

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Antiviral Activity:	The antiviral effect of PAXLOVID was demonstrated by a significant reduction in SARS-CoV-2 viral RNA concentration from baseline (Day 1) to Day 5 across the 3 Phase 2/3 (Section 5.1).	
Viral Sequencing:	Viral sequencing analysis showed that Delta was the most prevalent VOC in pivotal Study EPIC-HR and supportive interim analysis Study EPIC-SR. Omicron was the most prevalent VOC in supportive Study EPIC-PEP. To date, PAXLOVID treatment does not select for mutations in the M^{pro} gene.	
Risks and Risk Management with PAXLOVID		
Safety during use in Pregnancy and Lactation	There were no nirmatrelvir-related severe manifestations of developmental toxicity (malformations and embryo-fetal lethality) at the highest dose tested in rats and rabbits and no nirmatrelvir-related adverse effects on pre- and post-natal development up to the highest dose tested in rats. Across the PAXLOVID clinical studies there were 7 cases of Maternal exposure during pregnancy – in 4 of the 7 cases, female study participants received placebo, in 3 of the 7 cases the pregnancies occurred in female partners of male study participants receiving PAXLOVID. There were no associated AEs in any of the 3 cases. In all 3 cases the outcome of the pregnancies was unknown at the time of reporting.	No pregnancy studies have been conducted with PAXLOVID to date. Several Phase 1 studies are planned or ongoing. • A multiple dose open-label PK study of PAXLOVID in healthy lactating women (Study 1039) is ongoing. • An open-label study to evaluate the PK, safety, and tolerability of PAXLOVID in pregnant women with mild-to-moderate COVID-19 is ongoing (Study 1035). A post-authorization safety study (Study 1038) is planned to evaluate the safety of PAXLOVID in pregnant women and their infants using administrative healthcare claims data in the US.

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
	A cumulative search of post-marketing AE reports for cases reporting pregnancy or lactation through 31 December 2022 identified a total of 98 cases of Exposure during pregnancy and 14 cases involving lactation. • Of the 98 cases of Exposure during pregnancy, the trimester of exposure was unknown in 19 cases. In 13, 35, and 31 cases, exposure occurred during the first, second, and third trimester of pregnancy, respectively. Infant outcome was reported in 8 cases: normal in 4 babies, 1 baby was born prematurely at 29+1 weeks and was hospitalized in the neonatal intensive care unit due to prematurity of birth (no abnormalities reported), spontaneous abortion was reported 4 days after the end of Paxlovid course in 1 case, 1 case reported neonatal respiratory failure (APGAR Score was 1, 8, 9, no other information on infant outcome provided) and congenital anomalies of brachial cyst and anal fistula were reported in an infant exposed during 7th month of pregnancy. • A total of 14 cases involved lactation (Suppressed lactation [3 cases]; Lactation disorder [1 case] and Exposure via breastmilk [10 cases]). • Based on review of available pregnancy and lactation data, no update to the label is considered at the current time.	• A similar post-authorization safety study is also planned in Europe and United Kingdom (Study 1037).

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Safety in Patients with Renal Impairment	The safety profile in patients with mild or moderate renal impairment is sufficiently characterized and any potential risks are appropriately mitigated through the dosing recommendations (34 participants in Study EPIC-HR with moderate renal impairment and 2 participants with severe renal impairment). 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 An outpatient treatment study in severe renal impairment (Study 1028, EPIC-SRI), is ongoing.	PAXLOVID can be safely prescribed and used in patients with mild-moderate renal impairment as evidenced in Study EPIC-HR. Ongoing studies will provide guidance for use in patients with severe renal impairment.
Safety in Patients with Hepatic Impairment	PAXLOVID has an acceptable safety and tolerability profile in adult participants with normal hepatic function as well as those with moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in participants with severe hepatic impairment (Child-Pugh Class C);	PAXLOVID can be safely prescribed and used for patients with normal hepatic function and moderate hepatic impairment as evidenced in study data. As there is no pharmacokinetic data available for PAXLOVID for those with severe hepatic impairment, PAXLOVID is not recommended for use in patients with severe hepatic impairment.

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Drug-Drug Interactions	The use of ritonavir as PK enhancer for nirmatrelvir treatment of COVID-19 can result in drug-drug interactions with products metabolized by the CYP3A4 and CYP2D6 pathways or transported by P-gp. However, treatment with PAXLOVID is for a short-term duration (5 days). It is expected that the clinical management of potentially significant drug interactions for treatment of COVID-19 may be different compared to the current ritonavir labels which are meant for use of ritonavir as a PK enhancer for chronic HIV or HCV treatment as the duration of treatment is shorter. Amongst an estimated 8.6 million patient exposures in the US, the reporting rate is low (0.005%) and primarily represented by nonserious events that are consistent with the known profile of PAXLOVID.	As labeling extensively and adequately describes the interactions between PAXLOVID and other drugs dependent on the CYP3A4, CYP2D6 and P-gp pathway for clearance, prescribers are provided guidance on management of drug-drug interactions. Additionally, risk mitigation activities have been implemented to inform healthcare providers about appropriate patient selection and prescribing of PAXLOVID. See Risk Management section below for further detail.
Rebound	The phenomenon of VLR was observed in both PAXLOVID and placebo treatment groups with no differences observed in rates across both EPIC-HR and EPIC-SR studies. Rebounds were not associated with the recurrence of severe disease, emergence of resistant mutations or treatment failure. Literature on COVID-19 demonstrated a consistently low rate of COVID-19 rebound, lack of association with severe disease/hospitalization and lack of association with treatment.	Based on review of rebound in post-marketing reports, clinical studies and the available literature, there is no safety concern associated with viral rebound and is not associated with PAXLOVID treatment. A brief return of symptoms may be part of the natural history of SARS-CoV-2 infection in some persons, independent of treatment with PAXLOVID and regardless of vaccination status.[27]

Table 24. Medical Need and Benefit-Risk Summary for PAXLOVID and Treatment of Patients at Increased Risk of Developing Severe COVID-19

Dimension	Evidence and Uncertainties	Conclusion and Reasons
Risk Management	Uncertainties exist relating to use of PAXLOVID in special patient populations, including lack of safety data for patients with severe renal impairment, severe hepatic impairment, use of PAXLOVID in pregnancy and lactation. Ongoing routine pharmacovigilance supports the detection and further characterization of risks associated with PAXLOVID, including wrong dose medication errors and the risk for drug-drug interactions.	Ongoing routine pharmacovigilance and planned post-authorization safety studies aim to characterize safety in special populations. Extensive and adequate labeling guides, and appropriate patient selection for managing drug-drug interactions and supporting appropriate use of PAXLOVID. In addition, risk mitigation activities have been implemented, and will be sustained. Please see Section 6.4 for detail on implemented and proposed risk mitigation activities.
Conclusion Regarding Benefit-Risk Overall, the potential benefits and risks, as assessed by the efficacy and safety profile for PAXLOVID in the treatment of either vaccinated or unvaccinated patients with symptomatic COVID-19 who are at high risk of progressing to severe disease, demonstrate a clearly favorable profile. This is observed through reduction in COVID-19-related hospitalization or death, reductions in viral RNA levels, alleviation, and resolution of COVID-19-related signs and symptoms, and reduction in utilization of healthcare resources among individuals with COVID-19. Although there is a risk of drug-drug interactions with PAXLOVID therapy, amongst an estimated 8.6 million patient exposures in the US, the reporting rate is low (0.005%) and primarily represented by nonserious events that are consistent with the known safety profile. Risk mitigation activities have been implemented to inform healthcare providers about appropriate use of PAXLOVID. The public health impacts also weigh in favor of an NDA approval of the product.		

9.1. Benefits

COVID-19 is a serious and potentially fatal or life-threatening human infection. Based on clinical data to date, it is expected that PAXLOVID will be an effective antiviral agent against known VOC as confirmed by generated nonclinical data (Section 2.5.2).

The IA for the pivotal Study EPIC-HR, conducted at ~45% of participants (1294), met pre-specified efficacy criteria; data from the IA comprise the primary statistical interpretation for Study EPIC-HR. Both the primary and the first key secondary analyses showed significant treatment benefit ($p<0.0001$) in a sequential testing procedure pre-specified in the protocol. The relative reduction in COVID-19-related hospitalization and/or death from any cause through Day 28 was 89.1% when treatment was initiated within 3 days of symptom onset, and 84.3% when treatment was initiated within 5 days of symptom onset. The relative risk reduction was similar for the LPLV analysis being 89.1%, and 85.8%, respectively. Overall, the LPLV analysis confirmed the results from the ~45% IA. Furthermore, the overall treatment effect was similar for the participants included in the IA and participants included post-IA.

The treatment benefit reflected the antiviral effect demonstrated by PAXLOVID across all 4 Phase 2/3 Studies. In pivotal Study EPIC-HR, the antiviral effect of PAXLOVID was demonstrated by significant reduction in SARS-CoV-2 viral RNA levels compared with placebo, with an adjusted mean difference (SE) of 0.777 (0.081) $\log_{10}$ copies/mL reduction (~6-fold reduction) among participants treated within 5 days of symptom onset and no mAb treatment (mITT1, $p<0.0001$) (Section 5.1).

- As both the primary analysis and key secondary analysis of the primary endpoint for COVID-19-related hospitalization or death were met, time from symptom onset to initiation of treatment did not negatively affect the antiviral efficacy of PAXLOVID, with treatment indicated for use in participants with COVID-19 symptom onset ≤5 days.

- In an integrated analysis of data from Study EPIC-SR (vaccinated high-risk participants) and Study EPIC-HR (unvaccinated high-risk participants), PAXLOVID significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo in non-hospitalized symptomatic adult participants with COVID-19 who were either vaccinated or unvaccinated, and at increased risk of progression to severe disease, demonstrating an 83.0% relative risk reduction when treatment was initiated within 5 days of symptom onset ($p<0.0001$).

    - In vaccinated high-risk participants enrolled in supportive interim analysis Study EPIC-SR, treatment with PAXLOVID resulted in a non-statistically significant reduction in the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared to placebo in non-hospitalized symptomatic adult participants with COVID-19 who were at standard risk of progression to severe illness, demonstrating a 57.6% relative risk reduction in vaccinated participants who had ≥1 risk factor for severe COVID-19 illness (nominal $p=0.197$).

Treatment with PAXLOVID significantly reduced the duration of COVID-19 signs and symptoms compared with placebo.

- In pivotal Study EPIC-HR, treatment with PAXLOVID within 5 days of symptom onset significantly shortened the median time to sustained alleviation of all targeted COVID-related symptoms from 15 days to 13 days (Section 4.3.1.5) and shortened the median time to sustained resolution of these symptoms from 19 days to 16 days (Section 4.3.1.6).

Through Day 34, fewer participants in the PAXLOVID group reported COVID-19-related medical visits compared to placebo, with a 73% relative risk reduction observed with treatment.

Finally, published real-world evidence from Israel, Hong Kong, and the US demonstrate that PAXLOVID is highly effective in reducing the risk of hospitalization or death from COVID-19 during the Omicron-predominant period and that it provides an important layer of protection on top of COVID-19 vaccination for high-risk individuals (see supportive literature in Section 7).

9.2. Risks

The reported safety data from the Integrated Safety Pool (Studies EPIC-HR and EPIC-SR) confirm that PAXLOVID has a favorable safety profile. No clinically meaningful changes in laboratory values, vital signs, or ECGs (including QTc) were observed with PAXLOVID administration.

The all-causality TEAEs that were most common (reported in ≥5% of participants in either treatment group) were in the SOCs of Investigations, Nervous System Disorders (most frequently reported was Dysgeusia), Gastrointestinal Disorders (most frequently reported was Diarrhoea), and Infections and infestations. The overall incidence of participants with all-causality treatment-emergent SAEs that started on or prior to the Day 34 visit was lower in the PAXLOVID treatment group (1.6%) compared with the placebo group (5.2%).

There were 16 deaths among participants in the Integrated Safety Pool, all of which occurred in the placebo group. Of these, 15 were unvaccinated participants from Study EPIC-HR who were at high risk of progressing to severe disease and 1 was a vaccinated participant from Study EPIC-SR who had multiple risk factors for COVID-19. Of the 16 deaths, 14 occurred during the active safety collection period (up to Day 34). The remaining 2 deaths occurred during the long-term follow-up period. Of the 16 deaths, 15 were related to the disease under study (TEAEs reported as COVID-19 pneumonia [9 participants], COVID-19 [3 participants], Pneumonitis [2 participants], and Acute respiratory failure [1 participant]) and none of these 15 deaths were considered by the investigator to be related to study intervention. There was one death that was not related to the disease under study and the cause of death was reported as sepsis with underlying relapsed acute myeloid leukemia.

Post-treatment increases in SARS-CoV-2 RNA levels (ie, viral RNA (load) rebound) in NP swabs have been observed on Day 10 or Day 14 in a subset of PAXLOVID and placebo

recipients in Study EPIC-HR. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients. For participants who showed a half $\log_{10}$ or greater increase relative to end of treatment and whose viral RNA was persisted through follow-up, the occurrence was 1.73% placebo and 2.32% PAXLOVID. In addition to these, some participants had transient half-$\log_{10}$ or greater increases relative to end of treatment, the occurrence was 2.34% placebo vs 4.64% PAXLOVID. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had NP viral RNA results <LLOQ at all study timepoints in both the treatment and post-treatment periods. Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. Post-treatment viral RNA rebound also was not associated with drug resistance as measured by M^{pro} sequencing. The clinical relevance of post treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

Across the PAXLOVID clinical studies there were 7 cases of Maternal exposure during pregnancy – in 4 of the 7 cases, female study participants received placebo, in 3 of the 7 cases the pregnancies occurred in female partners of male study participants receiving PAXLOVID. There were no associated AEs in any of the 3 cases. As of 31 December 2022, the outcome of the pregnancies in all 3 cases was unknown.

To describe the safety profile of PAXLOVID during pregnancy, a Phase 1, open-label study is ongoing to evaluate the PK, safety, and tolerability of PAXLOVID in pregnant women with mild-to-moderate COVID-19 (Study 1035). The sponsor is also proposing a US safety surveillance study using real world data to assess the risk to pregnancy and birth outcomes following exposure to PAXLOVID during pregnancy (Study 1038).

A cumulative search of post-marketing AE reports for cases reporting pregnancy or lactation through 31 December 2022 identified a total of 98 cases of Exposure during pregnancy and 14 cases involving lactation. Based on review of available pregnancy and lactation data, no update to the label is required at the current time. A Phase 1, multiple dose open-label PK study of PAXLOVID in healthy lactating women is currently ongoing (Study 1039).

Serious and unexpected AEs may occur that have not been previously reported with PAXLOVID.

Based on the totality of the safety data the sponsor has determined that PAXLOVID has an acceptable safety profile that supports a positive benefit-risk assessment for use in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The 5-day regimen of PAXLOVID was safe and well-tolerated across all studies. Additionally, the 10-day regimen of PAXLOVID in Study EPIC-PEP, was safe and well-tolerated.

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.

The sponsor has implemented risk mitigation activities to inform healthcare providers about appropriate prescribing, dosing, and dispensing of PAXLOVID in patients with moderate renal impairment. The sponsor has also communicated the risk of potential serious adverse reactions due to drug-drug interactions and commits to these risk mitigations remaining in place (for further details see Table 24).

9.3. Benefit-Risk Assessment - Conclusion

Overall, the potential benefits and risks, as assessed by the efficacy and safety profile for PAXLOVID in the treatment of either vaccinated or unvaccinated patients with symptomatic COVID-19 who are at high risk of progressing to severe disease, demonstrate a clearly favorable profile. This is observed in the EPIC studies through reduction in COVID-19-related hospitalization or death, reductions in viral RNA levels, alleviation, and resolution of COVID-19-related signs and symptoms, and reduction in utilization of healthcare resources among individuals with COVID-19.

The clinical results are further supported by real-world studies reporting evidence that demonstrates PAXLOVID is highly effective in reducing the risk of hospitalization or death from COVID-19 during the Omicron-predominant period in both vaccinated (with or without a booster) and unvaccinated individuals who test positive for SARS-CoV-2 and are at high risk for developing severe COVID-19 based on CDC criteria, and that earlier treatment may have greater clinical benefit. Consistent with its mechanism of action, this real-world protection has been shown across all Omicron subvariants evaluated to date, including BA.1, BA.2, BA.2.12.1, and BA.4/5. In the clinical trial setting, the occurrence of both virological and symptomatic rebound was similar between PAXLOVID treated and untreated patients, and emerging data have suggested that rebound is likely part of the natural course of COVID-19 and not related to treatment failure. Although there is a risk of drug-drug interactions with PAXLOVID therapy, amongst an estimated 8.6 million patient exposures in the US, the reporting rate is low (0.005%) and primarily represented by nonserious events that are consistent with the known safety profile. Risk mitigation activities have been implemented to inform healthcare providers about appropriate use of PAXLOVID.

The public health impacts and situational context also weigh in favor of an NDA approval of the product. Specifically, COVID-19 still causes 4000 to 5000 hospital admissions and 500 to 600 deaths each day in the US, the vast majority of which occur in high-risk individuals who are eligible for PAXLOVID—thus many of these hospitalizations and deaths remain preventable with prompt treatment with PAXLOVID. Finally, mAbs have shown erosion of protection against continuously emerging variants, uptake of mRNA bivalent vaccines has been relatively low, and mitigation measures have been largely lifted. Such events potentially leave a substantial proportion of individuals at high risk of severe COVID-19 being susceptible to new emerging variants and subvariants including Omicron sublineages BQ.1 and XBB.

The change from an EUA to approval of PAXLOVID under an NDA will further facilitate prescriber and patient awareness, education, and access, increasing PAXLOVID's impact on

both patients and the broader healthcare system by reducing COVID-19 related medical visits, hospitalizations, and deaths.

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11. APPENDICES

Appendix 1. Analysis Sets for Phase 2/3 Studies

Table 25. Analysis Sets for Study EPIC-HR

Population	Description
FAS	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
SAS	All participants who received at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received. A randomized but not treated participant was excluded from the safety analyses.
mITT	All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants were analyzed according to the study intervention to which they were randomized.
mITT1	All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days of COVID-19 onset. Participants were analyzed according to the study intervention to which they were randomized.
mITT2	All participants randomly assigned to study intervention, who took at least 1 dose of study intervention. Participants were analyzed according to the study intervention to which they were randomized.
PP	All participants in the mITT1 set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations were reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria were finalized prior to breaking the blind.

FAS=full analysis set; SAS = safety analysis set; PP=per protocol

Table 26. Analysis Sets for Study EPIC-SR

Population	Description
FAS	All participants randomly assigned to study intervention.
SAS	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analyzed according to the intervention they received.
mITT	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and with at least 1 postbaseline visit through Day 28 who were treated ≤3 days after COVID-19 symptom onset. Participants were analyzed according to the study intervention to which they were randomized.
mITT1	All participants randomly assigned to study intervention, who took at least 1 dose of study intervention and with at least 1 postbaseline visit through Day 28. Participants were analyzed according to the study intervention to which they were randomized.
PP	All participants in the mITT1 set without major protocol violations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations were reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria were finalized prior to breaking the blind.

FAS=full analysis set; SAS = safety analysis set; PP=per protocol

Table 27. Analysis Sets for Study EPIC-PEP

Population	Description
FAS	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
SAS	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received. A randomized but not treated participant was excluded from the safety analyses.
mITT	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and have a negative RT-PCR result at baseline. Participants were analyzed according to the study intervention they were randomized.
mITT1	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and had a positive RT-PCR result at baseline. Participants were analyzed according to the study intervention they were randomized.
mITT2	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19 illness. Participants were analyzed according to the study intervention they were randomized.
mITT3	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and had a negative, positive, or missing RT-PCR result at baseline. Participants were analyzed according to the study intervention they were randomized.
PP	All participants in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations were reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria were finalized prior to breaking the blind.

FAS=full analysis set; SAS = safety analysis set; PP=per protocol

Appendix 2. Table Outlining Established and Other Potentially Significant Drug Interactions with PAXLOVID

Table 28. 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.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias.
Antiarrhythmics	lidocaine (systemic) disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ PAXLOVID	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
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 coadministration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Avoid concomitant use. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	apixaban	↑ apixaban	dabigatran product label for further information. Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin, primidone	↓ PAXLOVID	Co-administration contraindicated due to potential loss of virologic response and possible resistance.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.
Antidepressants	bupropion trazodone	↓ bupropion and active metabolite hydroxybupropion ↑ trazodone	Monitor for an adequate clinical response to bupropion. Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate, itraconazole[a]	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ PAXLOVID	Avoid concomitant use of voriconazole. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or lifethreatening reactions in patients with renal and/or hepatic impairment.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information.

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ 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	↓ PAXLOVID	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered.
Antimycobacterial	bedaquiline rifabutin rifapentine	↑ bedaquiline ↑ rifabutin ↓ PAXLOVID	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction. Avoid concomitant use with PAXLOVID.
Antipsychotics	lurasidone, pimozide,	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias.
Antipsychotics	quetiapine clozapine	↑ quetiapine ↑ clozapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations. If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Coadministration contraindicated due to potential for postural hypotension.
Calcium channel blockers	amlodipine, diltiazem, felodipine,	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	nicardipine, nifedipine verapamil		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.
Cardiovascular agents	eplerenone ivabradine	↑ eplerenone ↑ ivabradine	Coadministration with eplerenone is contraindicated due to potential for hyperkalemia. Coadministration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances.
Cardiovascular agents	aliskerin, ticagrelor, vorapaxar, clopidogrel cilostazol	↑ aliskerin ↑ ticagrelor ↑ vorapaxar ↓ clopidogrel active metabolite ↑ cilostazol	Avoid concomitant use with PAXLOVID. Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ PAXLOVID	Coadministration contraindicated due to potential loss of virologic response and possible resistance.

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor elexacaftor/tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑ elexacaftor/tezacaftor /ivacaftor ↑ tezacaftor/ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more 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.
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. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. 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.
Herbal products	St. John's Wort (hypericum perforatum)	↓ PAXLOVID	Co-administration contraindicated due to potential loss of virologic response and possible resistance.

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Coadministration contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
Immunosuppressants	cyclosporine, tacrolimus, everolimus sirolimus	↑ cyclosporine ↑ tacrolimus ↑ everolimus ↑ sirolimus	Avoid use of PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended. Refer to the individual immunosuppressant product label for further information and obtain expert consultation from the patient's immunosuppressive therapy specialist. Avoid concomitant use of everolimus and sirolimus and PAXLOVID.
Janus kinase (JAK) inhibitors	tofacitinib,	↑ tofacitinib,	Dosage adjustment of tofacitinib and upadacitinib is recommended. Refer to the tofacitinib product label for more information

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	upadacitinib	↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting betaadrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitors	lomitapide	↑ lomitapide	Coadministration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions.
Migraine medications	eletriptan	↑ eletriptan	Coadministration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events (see section 4.3).
	ubrogepant	↑ ubrogepant	Coadministration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hyrdocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	methadone	↓ methadone	narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ suvorexant ↑ aripiprazole, ↑ brexpiprazole, ↑ cariprazine, ↑ iloperidone, ↑ lumateperone, ↑ pimavanserin	Avoid concomitant use of suvorexant with PAXLOVID. Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Pulmonary hypertension agents (PDE5 inhibitors) Pulmonary hypertension agents (sGC stimulators)	tadalafil (Adcirca®) riociguat	↑ tadalafil ↑ riociguat	Avoid concomitant use of tadalafil with PAXLOVID. Dosage adjustment is recommended for riociguat. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil, sildenafil, tadalafil, vardenafil	↑ avanafil ↑ sildenafil ↑ tadalafil, ↑ vardenafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established. Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID. Refer to individual product label for more information.
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme

Table 28. Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			sedation and respiratory depression.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	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.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia, and hyperkalemia.

a. Drug interaction studies conducted with PAXLOVID.