FDA Briefing Document

NDA# 217188

Drug name: nirmatrelvir tablets and ritonavir tablets copackaged for oral use

Applicant: Pfizer Inc.

Antimicrobial Drugs Advisory Committee Meeting

March 16, 2023

Division of Antivirals (DAV)/Office of Infectious Diseases (OID)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought PAXLOVID to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Contents 2
Table of Tables 3
Table of Figures 4
Glossary 5
1 Executive Summary/Draft Points for Consideration by the Advisory Committee 6
1.1 Purpose/Objective of the Advisory Committee Meeting 6
1.2 Context for Issues to Be Discussed at the AC 6
1.3 Brief Description of Issues for Discussion at the AC 6
1.4 Draft Points for Consideration 8
2 Introduction and Background 8
2.1 Background of the Condition/Standard of Clinical Care 8
2.2 Pertinent Drug Development and Regulatory History 9
3 Summary of Issues for the AC 10
3.1 Efficacy Issues 10
3.1.1 Sources of Data for Efficacy 11
3.1.2 Efficacy Summary 12
3.1.3 Efficacy Issues in Detail 18
3.2 Safety Issues 32
3.2.1 Sources of Data for Safety 32
3.2.2 Safety Summary 32
3.2.3 Safety Issues in Detail 36
4 References 40
5 Appendix 46
5.1 Literature Review on PAXLOVID Effectiveness RWE 46
5.1.1 RWE Literature Search Process (Steps and Numbers of Articles Remaining) 53
5.2 Drug Utilization Database Description 54

Table of Tables

Table 1. Phase 2/3 Clinical Studies to Support the Efficacy Assessments 11

Table 2. Proportion of Subjects With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-HR C4671005 13

Table 3. Time to Sustained Symptom Alleviation Through Day 28, Trial EPIC-SR C4671002 16

Table 4. Proportion of Subjects With COVID-19-Related Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-SR C4671002 16

Table 5. Change From Baseline to Day 5 in SARS-CoV-2 RNA Levels in Nasopharyngeal Samples (Log_{10} Transformed Copies/mL) 20

Table 6. Nirmatrelvir Activity Against SARS-CoV-2 Omicron Subvariants in Cell Culture 22

Table 7. EPIC-HR: Rates of Post-Treatment Viral RNA Rebound 27

Table 8. EPIC-HR: Proportions of PAXLOVID or Placebo Subjects With Viral RNA <LLOQ at Each Analysis Visit 28

Table 9. Symptom Rebound Analysis 30

Table 10. Symptomatic Viral RNA Rebound Analysis 31

Table 11. Overview of Adverse Events[a], Safety Population, Trials EPIC-HR[b], EPIC-SR[b], EPIC-PEP[c] 33

Table 12. Subjects With Common Adverse Events[a] Occurring at ≥1% Frequency, Safety Population, Trials EPIC-HR[b], EPIC-SR[b], and EPIC-PEP[c] 35

Table 13. Screening of the Identified Observational RWE Studies on Outpatient PAXLOVID Effectiveness 47

Table of Figures

Figure 1. Proportion of Subjects With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-HR C4671005 15

Figure 2. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples (mITT1 Analysis Set), According to Enrollment Year. Charts Show Mean Values and 95% Confidence Intervals 23

Figure 3. Rates of Post-treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) Observed in EPIC-HR and EPIC-SR 29

Glossary

AC	Advisory Committee
AE	adverse event
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
CDER	Center for Drug Evaluation and Research
CI	confidence interval
COVID-19	coronavirus disease 2019
CYP	cytochrome P450
DDI	drug-drug interaction
eGFR	estimated glomerular filtration rate
EC_{90}	90% effective concentration
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
IND	investigational new drug
LLOQ	lower limit of quantification
mAb	monoclonal antibody
mITT	modified intent-to-treat
M^{pro}	SARS-CoV-2 main protease
NDA	new drug application
NP	nasopharyngeal
OSE	Office of Surveillance and Epidemiology
PO	orally
QSP	quantitative systems pharmacology
RRR	relative risk reduction
RT-PCR	reverse transcription-polymerase chain reaction
RWE	real-world evidence
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
VA	Veterans Affairs

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the available data support a favorable benefit-risk assessment for the use of PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

1.2 Context for Issues to Be Discussed at the AC

COVID-19 is a serious and potentially life-threatening illness which can result in pneumonia, multiorgan failure, respiratory failure, and death. Remdesivir, administered by intravenous infusion daily for 3 days, is the only FDA-approved therapy currently available for the treatment of mild-to-moderate COVID-19 in adults or pediatric patients who are at high risk for progression to severe disease. PAXLOVID, an oral product, received an Emergency Use Authorization (EUA) on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and adolescents who are at high risk for progression to severe disease. Another oral drug, molnupiravir, is also authorized for emergency use for the treatment of mild-to-moderate COVID-19 in certain adults who are at high risk for progression of severe disease and for whom alternative antiviral therapies are not accessible or clinically appropriate.

COVID-19 has evolved since the beginning of the COVID-19 pandemic and when the PAXLOVID registrational clinical trials were conducted. Presently, most adults in the United States have either received one or more COVID-19 vaccine doses or have previously been infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19 (CDC 2020b; CDC 2022a). Likewise, the circulating SARS-CoV-2 variants have continuously evolved. The Omicron variant and subvariants became predominant in early 2022 and remain responsible for essentially all SARS-CoV-2 infections in the United States; no anti-SARS-CoV-2 monoclonal antibodies are currently authorized for emergency use for COVID-19 treatment because of nonsusceptibility to circulating Omicron subvariants. Finally, different clinical presentations of COVID-19 have become more well known, including persistent SARS-CoV-2 infection in severely immunocompromised individuals and COVID-19 rebound, which is characterized by a relapse of symptoms or SARS-CoV-2 detection after initial recovery. However, hospitalizations and deaths related to COVID-19 remain significant issues, especially among certain populations (e.g., elderly, immunocompromised), with about 4000 COVID-19-related deaths and 35,000 COVID-19-related hospitalizations each week in the United States in January 2023 (CDC 2020a).

1.3 Brief Description of Issues for Discussion at the AC

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

To support the proposed PAXLOVID indication, the Applicant conducted three Phase 2/3 trials which provide relevant clinical efficacy and safety data (Table 1). PAXLOVID contains ritonavir, a potent cytochrome P450 (CYP) 3A inhibitor, and all of these trials excluded individuals with current or expected

use of any medications that have drug-drug interactions (DDIs) with PAXLOVID that may lead to serious adverse reactions. In addition, the two treatment trials enrolled in 2021, and included very few immunocompromised subjects. Key findings from these trials are summarized below:

EPIC-HR evaluated 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19 in adults who were unvaccinated for COVID-19 and at high risk for progression to severe disease. Treatment with PAXLOVID demonstrated a 5.6% (95% confidence interval [CI]: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72%, 93%) relative reduction, compared to placebo in the mITT1 population for the primary efficacy endpoint of COVID-19-related hospitalization or death from any cause through Day 28 (Table 2). The most common adverse reactions in the PAXLOVID group were dysgeusia (4.6%) and diarrhea (3.0%).

EPIC-SR evaluated 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19 in adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease. The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of time to sustained symptom alleviation through Day 28. However, a numerically lower rate of COVID-19-related hospitalizations or deaths from any cause through Day 28 was observed in all randomized subjects and in the subgroup of vaccinated high-risk subjects. Safety findings were consistent with EPIC-HR.

EPIC-PEP evaluated 5 or 10 days of PAXLOVID versus placebo for the postexposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. The study failed to demonstrate any meaningful difference for the primary efficacy endpoint of symptomatic SARS-CoV-2 infection through Day 14. Safety findings were consistent with EPIC-HR, and similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups.

This AC briefing document for PAXLOVID summarizes key efficacy and safety issues to inform the AC's consideration of these issues, as outlined below.

Efficacy

- Efficacy of PAXLOVID in high-risk adults who are vaccinated against COVID-19 or previously infected with SARS-CoV-2.
- Efficacy of PAXLOVID in the setting of the SARS-CoV-2 Omicron variant.
- Optimal duration of PAXLOVID treatment in immunocompromised patients.
- Impact of PAXLOVID on COVID-19 rebound.

Safety

- Serious adverse reactions due to DDIs.

1.4 Draft Points for Consideration

1. Please comment on the strength of evidence for use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations:
   a. Individuals who are vaccinated against COVID-19 or previously infected with SARS-CoV-2.
   b. Individuals infected with the Omicron variant.
   c. Individuals who are immunocompromised.

   Please comment if additional data are needed in these populations.
2. Please comment on the strength of evidence for an association between use of PAXLOVID in the treatment of mild-to-moderate COVID-19 and 'COVID-19 rebound'. Please comment if additional data are needed.
3. Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

COVID-19 is a serious and potentially life-threatening illness, which can result in pneumonia, multiorgan failure, respiratory failure, and death. As of mid-January 2023, over 660 million cases and 6.7 million deaths have been reported globally (JHU 2020), with more than 101 million cases of COVID-19 and over 1 million COVID-19-related deaths in the United States (CDC 2020a).

Patients with COVID-19 can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe illness is defined as an oxygen saturation <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mmHg, a respiratory rate >30 breaths/minute, or lung infiltrates >50%. Critical illness is defined as individuals who have respiratory failure, septic shock, and/or multiorgan dysfunction (FDA 2022; NIH 2022a).

SARS-CoV-2 variants have emerged over time and continue to emerge. In November 2021, a new variant, Omicron, was detected in laboratories in Southern Africa (Viana et al. 2022). By late January 2022, it was estimated that the Omicron variant was responsible for more than 99% of SARS-CoV-2 infections in the United States (Lambrou et al. 2022). The Omicron variant and its numerous subvariants have been noted to have substantial evasion of neutralizing antibodies (Willett et al. 2022) and may be more transmissible when compared with previous variants of concern (Baker et al. 2022); however, the risk of severe disease or death may be lower (Adjei et al. 2022).

To date, remdesivir is the only FDA-approved therapy for the treatment of mild-to-moderate COVID-19 in nonhospitalized adults who are at high risk for progression to severe disease[1]. Remdesivir,

[1] See the Prescribing Information at https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf.

administered by intravenous infusion, is a nucleotide prodrug of an adenosine analog and binds to the viral RNA-dependent RNA polymerase/template complex and inhibits viral replication by terminating RNA transcription prematurely (NIH 2022d). Remdesivir retains neutralization activity in cell-based assays against the Omicron variant and its subvariants (NIH 2022d).

In December 2021, the FDA issued an EUA for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate[2]. Molnupiravir is the oral prodrug of N4-hydroxycytidine, a ribonucleoside which, after phosphorylation to the active triphosphate, incorporates into viral RNA by viral RNA-dependent RNA-polymerases resulting in an accumulation of errors in the viral genome leading to inhibition of replication (known as viral error catastrophe or viral lethal mutagenesis) (NIH 2022c).The National Institutes of Health guidelines panel currently recommends only using molnupiravir when PAXLOVID and remdesivir are not available or cannot be given (NIH 2022c).

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

2.2 Pertinent Drug Development and Regulatory History

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

The PAXLOVID proposed indication is for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The Applicant has conducted one pivotal clinical trial in adults who are at high risk for progression to severe COVID-19, C4671005 (EPIC-HR), to support the proposed indication. Additionally, data are available from two supporting clinical trials: C4671002 (EPIC-SR), which evaluated PAXLOVID for the treatment of mild-to-moderate COVID-19 in individuals who were either fully vaccinated or who had no risk factors for progression to severe COVID-19, and C4671006 (EPIC-PEP), which evaluated PAXLOVID used as post-exposure prophylaxis in adult household contacts of an individual with symptomatic COVID-19.

The PAXLOVID proposed dosage is 300 mg nirmatrelvir with ritonavir 100 mg PO twice daily for 5 days. The PAXLOVID 300 mg nirmatrelvir/100 mg ritonavir dose was initially chosen to achieve a target minimum nirmatrelvir concentration in plasma approximating the protein binding-adjusted EC_{90} value (292 ng/mL, 585nM) for anti-SARS-CoV-2 activity in cell culture, which was supported by antiviral activity data from a SARS-CoV-2 mouse model and simulations with a preliminary population PK model suggesting that >90% of subjects achieve a trough concentration above the nirmatrelvir EC_{90} value after

[2] See the EUA Fact Sheet at https://www.fda.gov/media/155054/download.

the first dose. The 5-day treatment duration was based on the viral dynamics of SARS-CoV-2 in a quantitative systems pharmacology (QSP) model. The PAXLOVID 300 mg nirmatrelvir/ritonavir 100 mg twice daily for 5 days dosage was studied in the EPIC-HR, EPIC-SR, and EPIC-PEP clinical trials. EPIC-PEP also studied PAXLOVID for 10 days.

In patients with moderate renal impairment (defined as an estimated eGFR ≥30 to <60 mL/min), the proposed PAXLOVID dosage is 150 mg nirmatrelvir with 100 mg ritonavir PO twice daily for 5 days. This recommendation is based on data from a renal impairment study (Study 1011) demonstrating increased nirmatrelvir systemic exposure (mean AUC_{inf} ~87% higher compared to normal renal function). Study 1011 also demonstrated a mean 204% increase in AUC_{inf} in subjects with severe renal impairment compared to subjects with normal renal function as well as a higher incidence of adverse events (AEs) in subjects with severe renal impairment. A safety and PK study evaluating PAXLOVID as treatment of mild-to-moderate COVID-19 in subjects with severe renal impairment (both requiring and not requiring hemodialysis) is ongoing. PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end-stage renal disease (eGFR <15 mL/min) receiving dialysis until additional data are available to determine the appropriate dosing regimen for this patient population.

The FDA issued an EUA for PAXLOVID on December 22, 2021, for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19, including hospitalization and death[3]. The EUA dosing regimen is PAXLOVID (nirmatrelvir 300 mg with ritonavir 100 mg) PO twice daily for 5 days in patients with normal renal function or mild renal impairment, and PAXLOVID (nirmatrelvir 150 mg with ritonavir 100 mg) PO twice daily for 5 days in patients with moderate renal impairment. This regimen was primarily supported by adult interim data from EPIC-HR, in which PAXLOVID was generally safe and well-tolerated and reduced the risk of COVID-19-related hospitalization or death from any cause through Day 28. Pediatric patients 12 years of age and older weighing at least 40 kg were included in the EUA because the adult dosing regimen was anticipated to be appropriate for this population based on population PK modeling, and this met the distinct regulatory criteria for an EUA[4] despite the lack of pediatric clinical data. However, to determine the optimal dose in the pediatric population, more data are needed from the ongoing clinical trial EPIC-PEDS (NCT05261139), which is evaluating PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk pediatric subjects.

3 Summary of Issues for the AC

3.1 Efficacy Issues

- Efficacy of PAXLOVID in high-risk adults who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2.
- Efficacy of PAXLOVID in setting of the SARS-CoV-2 Omicron variant.
- Optimal duration of PAXLOVID treatment in immunocompromised patients.
- Impact of PAXLOVID on COVID-19 rebound.

[3] See the PAXLOVID Fact Sheet at https://www.fda.gov/media/155050/download.
[4] According to Section 564(c) of the Federal Food, Drug and Cosmetic Act.

3.1.1 Sources of Data for Efficacy

Efficacy data in support of this NDA come from three Phase 2/3 trials, EPIC-HR (completed), EPIC-SR (ongoing), and EPIC-PEP (completed). Table 1 provides an overview of these three trials. The number of subjects reported in this Advisory Committee briefing document for the EPIC-HR and EPIC-SR analyses are lower than reported in the original EUA 105 CDER review document[5] and other publicly available materials (Hammond et al. 2022; Pfizer 2022) due to exclusion of data from four clinical trial sites [two EPIC-HR clinical trial sites and two EPIC-SR clinical trial sites (through the December 19, 2021 data cutoff)]. As part of the NDA review, FDA conducted clinical trial site inspections and other review activities to ensure data reliability. Based on these inspections and review activities, FDA requested that the data from four clinical trial sites be excluded from the final data analyses. Extensive EPIC-HR and EPIC-SR clinical trial data review performed by the Applicant and FDA did not identify additional data reliability concerns at the other 189 EPIC-HR sites or the other 173 EPIC-SR sites (through the December 19, 2021 data cutoff). Excluding these four sites from the EPIC-HR and EPIC-SR analyses did not change the overall efficacy or safety conclusions. Two clinical trial sites from EPIC-PEP matching the four EPIC-HR and EPIC-SR sites were also excluded.

Table 1. Phase 2/3 Clinical Studies to Support the Efficacy Assessments

Study Identifier	Study Title	Study Design	Treatment, Duration	Primary Endpoint	Number of Subjects Randomized
EPIC-HR (C4671005)	An interventional efficacy and safety, Phase 2/3, double-blind, two-arm study to investigate orally administered PAXLOVID compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.	Phase 2/3, MC, R, PC, DB	Arm 1: PAXLOVID every 12 hours for 5 days Arm 2: Placebo every 12 hours for 5 days	Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	1049 (Arm 1) 1064 (Arm 2)

[5] See the EUA 105 review at https://www.fda.gov/media/155194/download.

Study Identifier	Study Title	Study Design	Treatment, Duration	Primary Endpoint	Number of Subjects Randomized
EPIC-SR (C4671002)	An interventional efficacy and safety, Phase 2/3, double-blind, two-arm study to investigate orally administered PAXLOVID compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.	Phase 2/3, MC, R, PC, DB	Arm 1: PAXLOVID every 12 hours for 5 days Arm 2: Placebo every 12 hours for 5 days	Time to sustained alleviation of all targeted signs/symptoms through Day 28	544 (Arm 1) 531 (Arm 2) (data cutoff December 19, 2021)
EPIC-PEP (C4671006)	A Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study to evaluate the safety and efficacy of two regimens of orally administered PAXLOVID in preventing symptomatic SARS-CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19.	Phase 2/3, MC, R, PC, DB, DD	Arm 1: PAXLOVID every 12 hours for 5 days followed by placebo every 12 hours for 5 days Arm 2: PAXLOVID every 12 hours for 10 days Arm 3: Placebo every 12 hours for 10 days	Proportion of participants who develop a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 among participants who have a negative RT-PCR result at baseline	921 (Arm 1) 917 (Arm 2) 898 (Arm 3)

Source: FDA Reviewer's analysis; NDA 217188.
Abbreviations: COVID-19, coronavirus disease 2019; DB, double-blind; MC, multicenter; PC, placebo-controlled; DD, double-dummy; R, randomized; RAT, rapid antigen test; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

3.1.2 Efficacy Summary

EPIC-HR

EPIC-HR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19, who were unvaccinated against COVID-19 and at high risk for progression to severe disease. Risk factors for progression to severe disease included: diabetes, overweight (body mass index >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID (nirmatrelvir 300 mg with ritonavir 100 mg) or placebo PO

twice daily for 5 days. Randomization was stratified by geographic region and whether participants had received or were expected to receive anti-SARS-CoV-2 therapeutic mAb treatment (yes/no) at the time of randomization. The total study duration was up to 24 weeks. The study was terminated early for efficacy based on prespecified interim analysis specifications.

A total of 2113 subjects were randomized. Baseline demographics and disease characteristics were as follows: mean age of 45 years; 51% male; 71% white, 4% black or African American, 15% Asian; 41% Hispanic or Latino; 67% had onset of symptoms ≤3 days at baseline; 49% SARS-CoV-2 seronegative at baseline; mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.89); 6% either received or expected to receive anti-SARS-CoV-2 therapeutic mAb treatment at baseline. The baseline demographic and disease characteristics were balanced between the two arms.

The primary efficacy endpoint was the proportion of subjects with COVID-19-related hospitalization or death from any cause through Day 28 (Table 2). The analysis was conducted in the modified intent-to-treat (mITT) population (all randomized subjects who took at least one dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset), the mITT1 population (all randomized subjects who took at least one dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset), and the mITT2 population (all randomized subjects who took at least one dose of study intervention were dosed ≤5 days of COVID-19 symptom onset). Table 2 shows analyses for the primary endpoint. Treatment with PAXLOVID demonstrated a 5.6% (95% CI: -7.3% to -4.0%; p<0.0001) absolute reduction, or 86% (95% CI: 72% to 93%) relative reduction compared to placebo, in the mITT1 population. All three analyses had p-values <0.0001.

Table 2. Proportion of Subjects With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-HR C4671005

mITT: All subjects randomly assigned to study intervention, who took at least one dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤3 days of COVID-19 symptom onset		
	PAXLOVID N=671	**Placebo N=647**
Subjects with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[a]	-6.1 (-8.2, -4.1)	
Two-sided nominal p-value	<0.0001	

mITT1: All subjects randomly assigned to study intervention, who took at least one dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤5 days of COVID-19 symptom onset		
	PAXLOVID N=977	**Placebo N=989**
Subjects with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[a]	-5.6 (-7.3, -4.0)	
Two-sided nominal p-value	<0.0001	
mITT2: All subjects randomly assigned to study intervention who took at least one dose of study intervention and were dosed ≤5 days of COVID-19 symptom onset		
	PAXLOVID N=1038	**Placebo N=1053**
Subjects with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[a]	-5.4 (-7.0, -3.8)	
Two-sided nominal p-value	<0.0001	

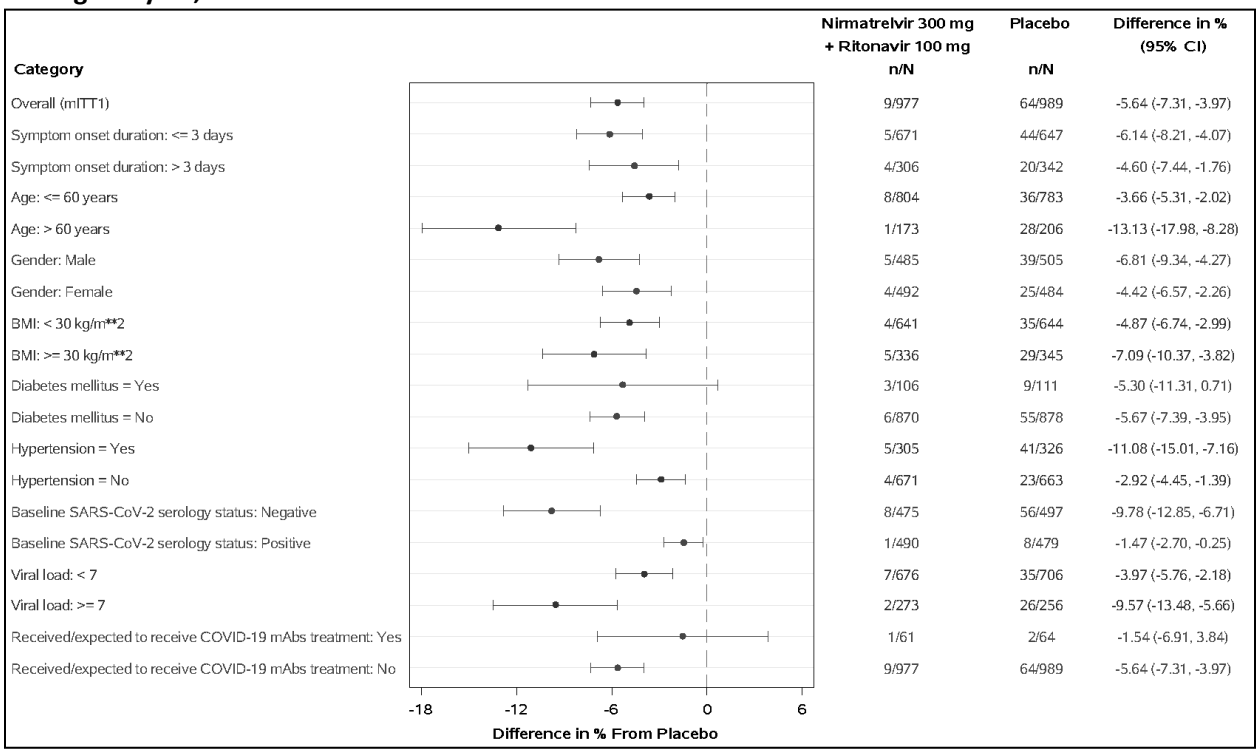
Source: FDA Reviewer's analysis of the ADTTE dataset; NDA 217188.

[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; mITT, modified intent-to-treat

Similar trends for the COVID-19-related hospitalization and death endpoint were observed across subject subgroups (Figure 1).

Figure 1. Proportion of Subjects With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-HR C4671005



Source: Applicant's Figure 84a.67a.3 submitted on December 5, 2022; NDA 217188.
All categories are based on the mITT1 population, except for COVID-19 mAb treatment, which is based on the mITT2 population.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; mITT, modified intent-to-treat; SARS-CoV-2; severe acute respiratory syndrome coronavirus-2

The PAXLOVID group demonstrated significant differences compared to the placebo group in secondary endpoint analyses of time to sustained symptom alleviation through Day 28, time to sustained symptom resolution through Day 28, proportion of subjects with COVID-19-related medical visits through Day 34, and death from any cause through Week 24. However, some secondary endpoints should be interpreted with caution. The endpoints of time to sustained symptom alleviation and time to sustained symptom resolution were influenced by the hospitalization and death events, as those events were considered symptom not alleviated/resolved until Day 28 and were not balanced between the two arms. The symptom-related analyses have limitations including high percentage of missing data (19% of treated subjects missed more than 25% of symptom diary entries) and uncertainty in the durability and potential clinical benefit using the sustained symptom alleviation/resolution definitions. The clinical meaningfulness of a reduction in COVID-19-related medical visits is not clear, and this endpoint is also influenced by hospitalization events.

EPIC-SR

EPIC-SR was a randomized, double-blind, placebo-controlled Phase 2/3 global trial for the treatment of adult outpatients with mild-to-moderate COVID-19. The study enrolled COVID-19-vaccinated subjects who were at high risk for progression to severe disease and unvaccinated subjects who had no risk factors for progression to severe disease. The third interim analysis utilizing the December 19, 2021

dataset (100% planned enrollment through protocol amendment 4) was submitted to support this NDA. Subjects with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within 5 days were randomized 1:1 to receive PAXLOVID (nirmatrelvir 300 mg with ritonavir 100 mg) or placebo PO twice daily for 5 days. Randomization was stratified by geographic region, vaccination status, and COVID-19 symptom onset (≤3 days versus >3 days). The total study duration was up to 24 weeks.

A total of 1075 subjects were randomized to receive PAXLOVID or placebo for 5 days. Of these, 59% were fully vaccinated high-risk subjects. Similar to EPIC-HR, there was a high percentage of missing symptom diary data (15% treated subjects missed more than 25% symptom diary entries) in EPIC-SR. The trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of time to sustained symptom alleviation through Day 28 in the mITT population (Table 3).

Table 3. Time to Sustained Symptom Alleviation Through Day 28, Trial EPIC-SR C4671002

mITT: All subjects randomly assigned to study intervention who took at least one dose of study intervention and were dosed ≤3 days of COVID-19 symptom onset		
Parameter	**PAXLOVID N=397**	**Placebo N=388**
Subjects with sustained symptom alleviation by Day 28, n (%)	289 (72.8)	286 (73.7)
Median time to sustained symptom alleviation (95% CI)	12 (11, 13)	14 (12, 15)
Two-sided p-value	0.4430	

Source: FDA Reviewer's analysis of the ADTTESS dataset; NDA 217188.
P-values calculated by log-rank test
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic

Table 4 displays analysis results for the prespecified secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. There was no statistically significant difference between the PAXLOVID arm and the placebo arm. However, a numerically lower hospitalization/death rate was observed in all randomized subjects and in the subgroup of vaccinated high-risk subjects in the PAXLOVID arm. None of the five hospitalized PAXLOVID subjects was in the intensive care unit. Three of the ten hospitalized placebo subjects were admitted to the intensive care unit. There was one death reported in the study, which was from the placebo arm.

Table 4. Proportion of Subjects With COVID-19-Related Hospitalization or Death From Any Cause Through Day 28, Trial EPIC-SR C4671002

mITT1: All subjects randomly assigned to study intervention who took at least one dose of study intervention		
	PAXLOVID N=540	**Placebo N=528**
Subjects with event, n (%)	5 (0.9)	10 (1.9)
COVID-19 hospitalization	5 (0.9)	10 (1.9)
Death	0	1 (0.2)
Estimated percentage difference in proportion (95% CI)[a]	-1.0 (-2.4, 0.5)	
Two-sided nominal p-value	0.1815	

Vaccinated high-risk subgroup of mITT1		
	PAXLOVID N=317	**Placebo N=314**
Subjects with event, n (%)	3 (0.9)	7 (2.2)
COVID-19 hospitalization	3 (0.9)	7 (2.2)
Death	0	1 (0.3)
Estimated percentage difference in proportion (95% CI)[a]	-1.3 (-3.3, 0.7)	
Two-sided nominal p-value	0.1970	

Source: FDA Reviewer's analysis of the ADTTE dataset; NDA 217188.

[a] The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; mITT, modified intent-to-treat

EPIC-SR was reopened in March 2022, implementing protocol amendment 5, which expanded enrollment to collect information on the hospitalization/death endpoint in the setting of the Omicron variant, enrolling subjects who had no risk factors for progression to severe disease and who had not received any COVID-19 vaccines in the prior 12 months. Enrollment was terminated in June 2022 due to no hospitalization/death events observed after reopening. Additional datasets including the 287 subjects enrolled in 2022 were submitted to the NDA to support the analyses on COVID-19 rebound assessment (see the subsection *Impact of PAXLOVID on COVID-19 Rebound*, below).

EPIC-PEP

EPIC-PEP was a randomized, double-blind, double-dummy, placebo-controlled Phase 2/3 global trial for postexposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. Subjects with a negative screening SARS-CoV-2 rapid antigen test result and who were asymptomatic household contacts of a symptomatic individual who recently tested positive for SARS-CoV-2 were enrolled. Eligible subjects were randomized 1:1:1 to receive PAXLOVID (nirmatrelvir 300 mg with ritonavir 100 mg) PO twice daily for 5 days (followed by placebo for 5 days), PAXLOVID (nirmatrelvir 300 mg with ritonavir 100 mg) PO twice daily for 10 days, or placebo for 10 days. Randomization was stratified by presence of risk factors associated with severe COVID-19 illness and geographic region. The total study duration was up to 42 days.

A total of 2736 subjects were randomized. The primary efficacy endpoint was symptomatic reverse transcription-polymerase chain reaction (RT-PCR)- or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14. Among subjects who had a negative RT-PCR result at baseline (mITT population), event rates were 22/844 (2.6%), 20/830 (2.4%) and 33/840 (3.9%) in the PAXLOVID 5-day arm, PAXLOVID 10-day arm, and placebo arm, respectively. The difference between each PAXLOVID arm and placebo arm was not clinically meaningful and was not statistically significant at a two-sided level of 0.05. Each arm had one COVID-19-related hospitalization event. The two subjects from PAXLOVID arms with hospitalization events had positive RT-PCR results at baseline (not in the mITT population). The subject from the placebo arm with a hospitalization event had negative RT-PCR result at baseline (in the mITT population). No deaths were reported in this study.

3.1.3 Efficacy Issues in Detail

Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Previously Infected With SARS-CoV-2

Background

The proposed PAXLOVID indication is for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or prior SARS-CoV-2 infection. However, EPIC-HR, the pivotal trial which demonstrated an 86% relative risk reduction (RRR) for PAXLOVID in the endpoint of COVID-19-related hospitalization or death from any cause through Day 28 (mITT1 population), enrolled high-risk adults who had not received any dose of a COVID-19 vaccine and who had not had a prior confirmed SARS-CoV-2 infection. Because COVID-19 vaccination is known to reduce the risk of severe disease[6], the relevance of the benefit with PAXLOVID observed in EPIC-HR to high-risk adults with pre-existing SARS-CoV-2 immunity was an important review issue.

Currently, the overwhelming majority of adults in the United States have either received one or more COVID-19 vaccine doses or previously been infected with SARS-CoV-2. As of January 26, 2023, 91% of the total U.S. population ≥18 years of age, and 95% of the U.S. population ≥65 years of age, had received at least one COVID-19 vaccine dose[7]. In addition, 79% of the total U.S. population ≥18 years of age, and 94% of the population ≥65 years of age, had completed a COVID-19 primary vaccination series. Furthermore, the results from EPIC-PEP, which enrolled from September 9, 2021, to April 12, 2022 (a later enrollment period than for EPIC-HR), indicate that even unvaccinated adults were likely to be SARS-CoV-2 seropositive by 2022, presumably from prior infection. In EPIC-PEP, which enrolled adults with negative screening SARS-CoV-2 rapid antigen test results and who were asymptomatic household contacts of individuals with COVID-19, only 12% of subjects reported receiving at least one COVID-19 vaccine dose, but 91% were SARS-CoV-2 seropositive at baseline.

Assessment

Methods

In order to assess the benefit of PAXLOVID treatment in high-risk adults who were previously vaccinated against COVID-19 or previously infected with SARS-CoV-2, EPIC-HR and EPIC-SR efficacy data were analyzed using the following subgroups of subjects who had been treated within 5 days of symptom onset and who had at least one risk factor that put them at high risk for progression to severe disease:

1. **Vaccinated high-risk subgroup in EPIC-SR**.
    a. EPIC-SR was underpowered to detect a treatment effect in this subgroup. Once PAXLOVID received an EUA in December 2021 for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of vaccination status, there was a lack of clinical equipoise to continue enrolling these subjects into a placebo-controlled trial, as vaccinated high-risk individuals could

[6] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/index.html.
[7] See https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-count-pop12; accessed September 27, 2022.

obtain PAXLOVID outside of a trial setting. Consequently, this analysis is limited to 631 vaccinated high-risk subjects who were enrolled prior to PAXLOVID receiving an EUA.

2. **Seropositive subgroup in EPIC-HR**, to represent high-risk adults who may have previously been infected with SARS-CoV-2 and as a surrogate for vaccinated adults.
    a. Baseline SARS-CoV-2 seropositivity may indicate some pre-existing SARS-CoV-2 immunity due to prior infection. Although immunity from prior infection is not identical to immunity from prior vaccination, the seropositive subgroup could be considered the EPIC-HR subgroup most representative of COVID-19 vaccinated adults. Analyses in this subgroup were considered supportive of the PAXLOVID EUA for the treatment of mild-to-moderate COVID-19 in high-risk individuals regardless of COVID-19 vaccination status.
3. **Seronegative subgroup in EPIC-HR**, for comparison.

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

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

- **EPIC-SR vaccinated high-risk subgroup**: 3/317 (<1%) PAXLOVID recipients versus 7/314 (2%) placebo recipients met the composite endpoint, for a RRR of 58% (nominal p-value=0.2).
- **EPIC-HR seropositive subgroup**: 1/490 (<1%) PAXLOVID recipients versus 8/479 (2%) placebo recipients met the composite endpoint, for a RRR of 88% (nominal p-value=0.02).
- **EPIC-HR seronegative subgroup**: 8/475 (2%) PAXLOVID recipients versus 56/497 (11%) placebo recipients met the composite endpoint, for a RRR of 85% (nominal p-value<0.0001).

P-values were based on difference in estimated proportions using the Kaplan-Meier method.

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

Nasopharyngeal Viral RNA Changes Over Time

In exploratory analyses, PAXLOVID treatment led to significantly greater reductions in nasopharyngeal (NP) SARS-CoV-2 viral RNA levels compared to placebo from baseline to Day 5 in all three subgroups, although baseline viral RNA levels were numerically higher overall in the EPIC-HR seronegative subgroup. The Applicant conducted a statistical analysis of change from baseline to Day 5 in $\log_{10}$ transformed viral RNA levels (copies/mL) from NP samples. The analysis of covariance model included treatment, geographic region, symptom onset duration (≤3, >3 days), and baseline viral RNA level as

covariates. Baseline SARS-CoV-2 serology status was also a covariate in the EPIC-SR vaccinated high-risk subgroup analysis. PAXLOVID conferred an additional mean reduction (SE) of -0.84 (0.14) log_{10} copies/mL in the EPIC-SR vaccinated high-risk subgroup (p≤0.0001), -0.47 (0.12) log_{10} copies/mL in the EPIC-HR seropositive subgroup (p≤0.0001), and -1.01 (0.11) log_{10} copies/mL in the EPIC-HR seronegative subgroup (p≤0.0001). Please see Table 5. FDA analyses were consistent with the Applicant's findings.

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

Trial	EPIC-SR		EPIC-HR			
Subgroup	Vaccinated High-Risk		Seropositive		Seronegative	
Treatment	PAX	PBO	PAX	PBO	PAX	PBO
Baseline n	256	257	320	330	436	444
Baseline mean (SD)	6.21 (1.86)	6.00 (1.87)	4.75 (2.23)	4.45 (2.22)	6.54 (1.59)	6.50 (1.60)
Day 5 n	246	238	280	296	396	387
Day 5 mean (SD)	2.58 (1.76)	3.32 (2.02)	1.88 (1.70)	2.22 (1.98)	3.32 (1.65)	4.31 (2.06)
Change[a] from BL n	245	236	280	296	396	387
Change from BL mean (SE)[a]	-3.35 (0.23)	-2.51 (0.23)	-2.72 (0.09)	-2.26 (0.09)	-3.31 (0.17)	-2.30 (0.17)

Source: Information taken from the Applicant's Tables 84b.2.2.16.f and 84a.2.2.12 submitted to NDA 217188 on December 5, 2022.

[a] Least squares mean difference.

Abbreviations: BL, baseline; PAX, PAXLOVID; PBO, placebo; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation; SE, standard error

Real-World Evidence

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

Among the identified studies, five are based on appropriate source data and implemented design features that can account for the potential bias introduced by "index time" selection. These five retrospective cohort studies estimated the effectiveness of PAXLOVID by COVID-19 vaccination status, or in a vaccinated population only. In general, these studies had similar findings to the clinical trials (i.e., PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status). However, while the source data and certain design elements of these cohort studies were appropriate, there were insufficient details on the data source, methods, or analytical approach for a complete review to determine the quality of the results of the studies. Please see Section 5.1 for more details.

Conclusion

The EPIC-HR and EPIC-SR clinical trial results support the efficacy of PAXLOVID for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. While pre-existing SARS-CoV-2 immunity, either from vaccination or prior infection, is among the factors that impact the risk of progression to severe COVID-19, the relative risk reduction with PAXLOVID versus placebo for COVID-19-related hospitalization or death from any cause

appears to be similar in high-risk subjects regardless of prior COVID-19 vaccination or baseline SARS-CoV-2 serostatus.

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

Background

The pivotal clinical trial EPIC-HR enrolled subjects in the timeframe of July to November 2021. During this period, the SARS-CoV-2 Delta variant was predominant in the United States and throughout most of the world, and this preceded the emergence of the SARS-CoV-2 Omicron variant and subvariants. As expected, the study population in EPIC-HR was primarily (~99%) infected with the SARS-CoV-2 Delta variant, and the Omicron variant was not observed.

Soon after the completion of EPIC-HR, the Omicron variant quickly became predominant and replaced the SARS-CoV-2 Delta variant in the United States and worldwide. Currently, Omicron subvariants are responsible for essentially all SARS-CoV-2 infections in the United States, with the subvariants BQ.1, BQ.1.1, and XBB.1.5 most commonly detected (CDC Nowcast, accessed February 1, 2023).

While the second half of the EPIC-SR trial was conducted from March to June 2022, in a study population primarily (~99%) infected with the SARS-CoV-2 Omicron variant (mostly BA.2-related subvariants), data from this trial were insufficient to directly determine the clinical efficacy of PAXLOVID in patients infected with the Omicron variant and at high risk for severe COVID-19. Enrollment during this period was restricted to subjects at low risk for severe disease given high-risk subjects could obtain PAXLOVID under EUA, and no subjects during this period reached the secondary efficacy endpoint of COVID-19-related hospitalization or death from any cause through Day 28.

Assessment

Despite the lack of clinical trial data to directly determine the clinical efficacy of PAXLOVID in high-risk adults infected with the SARS-CoV-2 Omicron variant, nonclinical and clinical data demonstrate that PAXLOVID retains antiviral activity against the SARS-CoV-2 Omicron variant. Using biochemical assays, the activity of nirmatrelvir was determined against recombinant SARS-CoV-2 M^{pro} enzymes containing naturally occurring amino acid polymorphisms, including P132H, a common polymorphism in the Omicron variant and subvariants. Nirmatrelvir retained activity (K_i fold-change <3) against SARS-CoV-2 M^{pro} enzymes with naturally occurring polymorphisms (e.g., G15S, T21I, L75F, K88R, L89F, K90R, P108S, P132H, T169S, and A260V). In cell culture, nirmatrelvir retained activity (EC_{50} value fold-change <3) against different SARS-CoV-2 variants, including Alpha, Gamma, Delta, Lambda, Mu, and Omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5 (Table 6). Literature reports have also indicated that nirmatrelvir retains activity against several SARS-CoV-2 variants in cell culture, including Omicron subvariants BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and XBB (Abdelnabi et al. 2022; Bojkova et al. 2022a; Bojkova et al. 2022b; Li et al. 2022; Ohashi et al. 2022; Saito et al. 2022; Takashita et al. 2022a; Takashita et al. 2022b; Takashita et al. 2022c; Vangeel et al. 2022; Imai et al. 2023). Nirmatrelvir was also demonstrated to have antiviral activity against other human coronaviruses in cell culture, including SARS-CoV-1, MERS-CoV, and HCoV-229E.

Table 6. Nirmatrelvir Activity Against SARS-CoV-2 Omicron Subvariants in Cell Culture

Variant	M^{pro} Polymorphism(s)	n	Geomean EC_{50} nM (Range)	EC_{50} Fold-Change	Geomean EC_{90} nM (Range)	EC_{90} Fold-Change
USA-WA1/2020	N/A	7	70 (49-98)	N/A	211 (123-478)	N/A
Omicron BA.2	P132H	5	65 (52-78)	0.9	132 (95-162)	0.6
Omicron BA.2.12.1	P132H	5	40 (34-44)	0.6	114 (72-408)	0.5
Omicron BA.4	P132H	3	39 (19-54)	0.6	98 (92-104)	0.5
Omicron BA.5	P132H	5	44 (29-117)	0.6	178 (109-451)	0.8

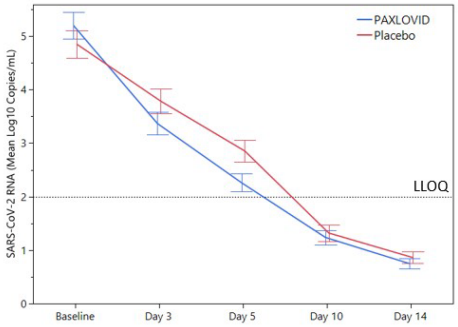
Source: Applicant's NDA 217188 nonclinical study reports. Data are from Vero E6-TMPRSS2 cells treated with a P-gp inhibitor.
Abbreviations: EC_{50}, 50% effective concentration; EC_{90}, 90% effective concentration; geomean, geometric mean; n, number of experiments; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

In addition, bioinformatic analyses of M^{pro} and M^{pro} cleavage site amino acid sequence conservation were provided based on the GISAID EpiCoV sequence database (n=12.7 million sequences, accessed November 30, 2022). Note that these analyses are affected by global disparities in SARS-CoV-2 genomic surveillance. Only 10 M^{pro} polymorphisms and 5 M^{pro} cleavage site polymorphisms were found to have a cumulative frequency ≥0.1%. Of the 10 M^{pro} polymorphisms, 8 did not significantly affect nirmatrelvir activity in biochemical assays, while 2 (L30I and T45N) have not yet been tested. The effects of the M^{pro} cleavage site polymorphisms have not been determined, but M^{pro} cleavage site substitutions outside of M^{pro} have not been associated with nirmatrelvir resistance in cell culture studies. Overall, these analyses demonstrate that SARS-CoV-2 M^{pro} and M^{pro} cleavage sites are highly conserved and that nirmatrelvir is likely to retain activity against circulating and emerging variants of SARS-CoV-2.

Lastly, analysis of viral RNA shedding data from EPIC-SR subjects who enrolled in the 2022/Omicron enrollment period (March to June 2022) found that PAXLOVID retained antiviral activity against the SARS-CoV-2 Omicron variant in treated subjects (Figure 2). Compared to placebo, PAXLOVID treatment was associated with a more rapid decline in viral RNA levels in NP samples in both the 2021/pre-Omicron enrollment period and in the 2022/Omicron enrollment period. In the 2021/pre-Omicron period, ~98% of subjects with available viral sequence data were infected with the SARS-CoV-2 Delta variant, similar to EPIC-HR, while in the 2022/Omicron period, ~99% of subjects with available data were infected with the SARS-CoV-2 Omicron variant (mostly BA.2-related subvariants).

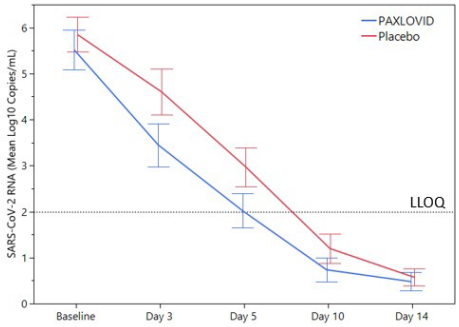
Figure 2. EPIC-SR: Analysis of SARS-CoV-2 RNA Levels (Log_{10} Copies/mL) in NP Samples (mITT1 Analysis Set), According to Enrollment Year. Charts Show Mean Values and 95% Confidence Intervals

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



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

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



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

Source: FDA analysis of ADMC and ADSL datasets; NDA 217188.
Abbreviations: BL, baseline; cp/mL, copies per milliliter; EOT, end-of-treatment; LLOQ, lower limit of quantification; mITT, modified intent-to-treat; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Conclusion

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

Through our monitoring of the RWE publications, we identified five retrospective cohort RWE studies that used appropriate source data and with acceptable design to estimate the effectiveness of PAXLOVID in reducing hospitalization and death from COVID-19 during periods when the SARS-CoV-2 Omicron variant was predominant. While these reports also indicate that PAXLOVID is likely to retain clinical efficacy against COVID-19 caused by the SARS-CoV-2 Omicron variant, these published studies do not provide sufficient information for a complete review to determine their quality (see Section 5.1 for additional details).

Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients With Mild-to-Moderate COVID-19

Background

The two Phase 2/3 COVID-19 treatment trials supporting the NDA, the pivotal trial EPIC-HR and the supportive trial EPIC-SR, evaluated 5 days of treatment with PAXLOVID versus placebo. EPIC-HR demonstrated an 86% relative risk reduction with 5 days of PAXLOVID treatment for the endpoint of COVID-19-related hospitalization or death from any cause through Day 28 among adults with laboratory-confirmed, symptomatic SARS-CoV-2 infection who had at least one risk factor that put them at high risk for progression to severe disease, who had not received any dose of a COVID-19 vaccine, and who began

treatment within 5 days of symptom onset. However, only 13/2246 subjects (<1%) in the full analysis set in EPIC-HR were classified as having immunosuppression.

Patients with moderate to severe immunocompromise might benefit from a longer treatment course of PAXLOVID based on the clinical course of COVID-19 in this population. While most people with mild-to-moderate COVID-19 are expected to clear their infection within 10 days of symptom onset, individuals with moderate to severe immunocompromise can remain infectious beyond 20 days (CDC 2022b). Persistent SARS-CoV-2 infection, defined as SARS-CoV-2 RNA detection ≥30 days after initial positivity, was reported in 14% (51/368) of subjects with hematologic malignancies who were diagnosed with COVID-19 from March 10, 2020 to February 28, 2021 at one center and were alive 30 days after their COVID-19 diagnosis (Lee et al. 2022); receipt of anti-CD20 therapy within the prior year, cellular therapy including hematopoietic stem cell transplantation within 1 year, and chronic lymphopenia were associated with persistent SARS-CoV-2 infection on multivariate analysis in this study. Risks of persistent SARS-CoV-2 infection include morbidity and mortality from COVID-19, interruption in treatment for cancer and other medical conditions, SARS-CoV-2 transmission to contacts, and the potential evolution of SARS-CoV-2.

Assessment

Currently available clinical trial data are limited on use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in patients with moderate-to-severe immunocompromise. As noted above, <1% of enrolled subjects in EPIC-HR were classified as having immunosuppression, six of whom were randomized to PAXLOVID versus seven to placebo. None of these 13 subjects experienced the primary outcome of COVID-19-related hospitalization or death from any cause through Day 28. SARS-CoV-2 viral RNA levels through Day 14 from these 13 immunosuppressed subjects were within the range seen in the overall population, with no evidence of increased levels after treatment ended on Day 5 among the PAXLOVID recipients.

Some (~20) severely immunosuppressed patients with prolonged persistent SARS-CoV-2 infection (up to 6 months) have received longer courses of PAXLOVID of 10 to 28-day duration under single patient INDs. Several of these patients have subsequently improved and tested negative for SARS-CoV-2 infection (Ford et al. 2022; Trottier et al. 2022). The small number of patients, combined with their variable use of other concurrent antiviral medications like remdesivir or anti-SARS-CoV-2 therapeutic mAb therapy and their variable health status at treatment initiation, precludes drawing any conclusions from these cases.

QSP modeling suggests a potential benefit for longer-duration PAXLOVID treatment (10 days) in viral RNA reduction in immunocompromised patients. The Applicant used QSP models and virtual populations to predict the optimal duration of treatment in both the overall PAXLOVID-eligible population and the immunocompromised population. This QSP modeling attempted to account for the effects of the immune system on SARS-CoV-2 replication in infected patients and was developed using longitudinal data from observational studies in SARS-CoV-2 infected subjects that measured immune markers in the blood (e.g., serum cytokine levels) and SARS-CoV-2 RNA levels in NP samples. Clinical trial data from studies of SARS-CoV-2 antiviral products (i.e., bamlanivimab/etesevimab, casirivimab/imdevimab, and molnupiravir) also informed the QSP model. The virtual immunocompromised patients were generated by two approaches: a mechanistic approach that attenuates Type I IFN and $CD8^+$ T cell-mediated killing of infected cells which induces a prolonged viral shedding profile, and a phenotypic approach that selects PAXLOVID-eligible virtual patients who exhibit

a long viral RNA shedding. QSP modeling of 5, 10, or 15 days of PAXLOVID treatment indicated the following: while extending treatment beyond 5 days in the overall PAXLOVID-eligible population under the EUA was not predicted to offer additional benefit for SARS-CoV-2 viral RNA suppression, this strategy could aid viral RNA clearance in the immunocompromised population, whose viral RNA was predicted to be approximately twice that of the overall PAXLOVID-eligible population by Day 5 of treatment. In the immunocompromised population model, 10 days of PAXLOVID treatment was predicted to be sufficient for optimal viral RNA suppression (although 5 days of PAXLOVID treatment was still predicted to decrease viral RNA more quickly than placebo). The QSP modeling data support investigating longer durations of PAXLOVID treatment in the immunocompromised population in a clinical trial setting, where the impact of longer treatment duration on DDI management can also be evaluated in this population.

Conclusion

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

Impact of PAXLOVID on COVID-19 Rebound

Background

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

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

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

Assessment

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

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

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

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

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

The Day 10/14 definition was considered the primary definition of viral RNA rebound given it identified subjects with any evidence of viral RNA rebound from Day 5 to either Day 10 or Day 14. These analysis parameters were intended to provide a sensitive means to detect occurrences of post-treatment increases in viral RNA levels, regardless of magnitude. Viral RNA levels over time in individual subjects were also characterized to assess for different patterns between PAXLOVID- and placebo-treated subjects, for example whether the magnitude of post-treatment viral RNA increases clearly differ between PAXLOVID- and placebo-treated subjects.

Rates of post-treatment viral RNA rebound in EPIC-HR are summarized in Table 7. Based on the Day 10/14 (LLOQ/0.5 Combined) definition, post-treatment viral RNA rebound was observed in 8.3% of PAXLOVID recipients and 5.7% of placebo recipients (p=0.04, Fisher's exact test, not adjusted for multiplicity). In both treatment groups, higher rates of viral RNA rebound relative to Day 5/EOT were observed at Day 10 compared to Day 14, indicating most observations of rebound occurred by Day 10. Viral RNA levels for individual subjects who met the definitions of viral RNA rebound showed substantial

heterogeneity in the viral RNA patterns, with no clear or consistent differences between PAXLOVID and placebo recipients in the RNA rebound patterns or magnitude of rebound.

While the Day 10/14 (LLOQ/0.5 Combined) definition showed a modest yet nominally significant higher rate of rebound overall in PAXLOVID recipients compared to placebo recipients, post-treatment (i.e., post-Day 5) viral RNA rebound was clearly not restricted to PAXLOVID recipients. Furthermore, calculated rates of viral RNA rebound could be biased by the greater impact of PAXLOVID on early viral RNA declines through Day 5. This definition would not capture subjects with viral RNA levels that declined slowly or remained relatively high through the treatment period (i.e., did not yet achieve a nadir level by Day 5).

Therefore, to compare post-treatment viral RNA rebound rates more directly between subjects with comparable on-treatment virologic responses, the Day 10/14 (LLOQ/0.5 Combined) analysis was restricted to PAXLOVID and placebo recipients who were considered Day 5/EOT Virologic Responders. In this subgroup of subjects, or in the smaller subset of subjects with viral RNA <LLOQ at Day 5, rates of viral RNA rebound after Day 5 remained higher in PAXLOVID recipients, but the differences were modest and no longer statistically significant (Table 7).

Table 7. EPIC-HR: Rates of Post-Treatment Viral RNA Rebound

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

Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
[a] Fisher's exact test, two-sided.
Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification

Regardless of any numeric differences in rates of post-treatment viral RNA rebound, PAXLOVID treatment ultimately did not result in delayed declines in viral RNA to unquantifiable levels. At all analysis visits, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ (Table 8). Based on these results, there is no indication that a positive SARS-CoV-2 RNA test result would be more likely for a PAXLOVID-treated patient, compared to an untreated patient, at any single cross-sectional timepoint through Day 14 (i.e., 9 days post-treatment).

Table 8. EPIC-HR: Proportions of PAXLOVID or Placebo Subjects With Viral RNA <LLOQ at Each Analysis Visit

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

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

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

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

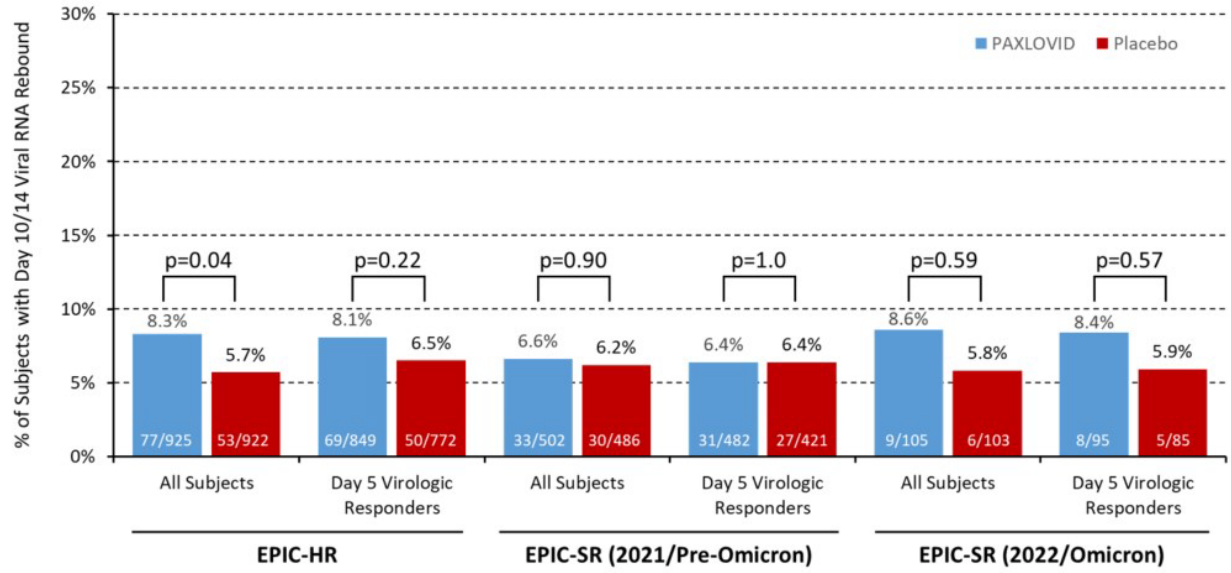
Post-treatment viral RNA rebound in EPIC-HR generally was not associated with the emergence of potential nirmatrelvir drug resistance, although there were 2 subjects (3% of the 60 PAXLOVID-treated subjects with viral RNA rebound and available viral sequence data) who had a treatment-emergent amino acid substitution detected in M^{pro} that is potentially associated with nirmatrelvir resistance, including E166V in one subject, and T304I in the second subject.

The Applicant also conducted analyses assessing for cell culture infectious virus in a subset of NP samples from subjects in EPIC-HR using two types of infectivity assays: a viral recovery assay and a viral titration immunoassay (i.e., median tissue culture infectious dose [$TCID_{50}$] assay). Positive cell culture infectivity results from Day 10 or Day 14 samples were observed for a small number of subjects who experienced post-treatment viral RNA rebound, including subjects treated with PAXLOVID or placebo.

In EPIC-SR, comparable rates of post-treatment viral RNA rebound were observed between PAXLOVID and placebo recipients, with no analyses indicating statistically significant differences in rebound rates between the two groups. Furthermore, although the numbers of subjects who had Omicron variants detected or who enrolled in the Omicron period were relatively small, there were no significant differences in rebound rates between PAXLOVID and placebo recipients regardless of whether they were determined to be infected with a SARS-CoV-2 Delta or Omicron variant, or more broadly were enrolled in the pre-Omicron or Omicron periods. As observed in EPIC-HR, viral RNA levels for individual subjects with post-treatment viral RNA rebound in EPIC-SR showed no obvious differences in the patterns or magnitude of viral RNA rebound between PAXLOVID and placebo recipients, either overall or within the 2021/pre-Omicron or 2022/Omicron enrollment periods. PAXLOVID treatment also did not result in delayed declines in viral RNA to unquantifiable levels; at all analysis visits through Day 14, and in both the 2021/pre-Omicron and 2022/Omicron periods, a similar or greater percentage of PAXLOVID recipients compared to placebo recipients had viral RNA <LLOQ.

Figure 3 summarizes the rates of post-treatment viral RNA rebound observed in EPIC-HR (conducted during the 2021/pre-Omicron period), EPIC-SR (2021/pre-Omicron period), and EPIC-SR (2022/Omicron period). While there are some modest numeric differences in some comparisons, in general, overall similar rates of post-treatment viral RNA rebound were observed between both trials, between the 2021/pre-Omicron and 2022/Omicron periods, and between PAXLOVID and placebo recipients.

Figure 3. Rates of Post-treatment Viral RNA Rebound (Day 10/14 [LLOQ/0.5 Combined]) Observed in EPIC-HR and EPIC-SR



Source: FDA analysis of the ADMC and ADSL datasets; NDA 217188.
P-Values based on Fisher's exact test, two-sided.
Abbreviation: LLOQ, lower limit of quantification

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

As with viral RNA rebound, calculated rates of symptom rebound can vary widely depending on the analysis parameters and available data timepoints. FDA analyses focused on measures of symptom rebound after achieving at least a short-term symptom recovery, using symptom data reported by study subjects in electronic diaries through Day 28 (i.e., 23 days post-treatment).

The following definitions were used in the symptom rebound analysis.

- **Short symptom recovery**: The first day of at least two consecutive diary entries where all targeted symptoms are absent (subjects hospitalized prior to short symptom recovery are considered as not having symptom recovery through Day 28).
- **Symptom rebound**: After achieving short symptom recovery, the first day of at least two consecutive diary entries where there is any targeted symptom (regardless of severity), or when a subject is hospitalized after symptom recovery. If a symptom rebound occurred on or before Day 5,

the subject is considered not recovered on the day of the symptom rebound, and reanalyzed for short symptom recovery and symptom rebound in the following days.

- **Moderate symptom rebound**: For those with symptom rebound, having (a) at least one rebound symptom being moderate or severe, (b) at least two symptoms of any severity during a day of rebound, or (c) a hospitalization/death event.

Rates of short symptom recovery, symptom rebound, and moderate symptom rebound are summarized separately for EPIC-HR, EPIC-SR 2021 (pre-Omicron period), and EPIC-SR 2022 (Omicron period) trials in Table 9.

Table 9. Symptom Rebound Analysis

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

Source: FDA analysis of the EPIC-HR and EPIC-SR ADSL/ADSO datasets; NDA 217188.
Subjects with no symptom data were not included in the analyses.
[a] Percentage over total subjects.
[b] Percentage over those who achieved short symptom recovery.
[c] Difference between two arms is not statistically significant; p-value=0.5589 by Pearson chi-squared test with continuity correction.
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in treatment arm

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

The relationship between viral RNA rebound and symptom rebound could not be fully investigated. The majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14. Furthermore, viral RNA data were not captured daily, while subject-reported symptoms could vary substantially from day-to-day.

Given these limitations in the combined virology and symptom data, cases of symptomatic viral rebound in EPIC-HR and EPIC-SR were identified based on the following definitions:

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

As shown in Table 10, cases of symptomatic viral RNA rebound were infrequent (<2% across both arms) with no consistent trend of a difference in rates between PAXLOVID and placebo recipients in EPIC-HR, and both the pre-Omicron and Omicron periods of EPIC-SR.

Table 10. Symptomatic Viral RNA Rebound Analysis

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

Source: FDA analysis of the EPIC-HR and EPIC-SR ADSL/ADMC/ADSO datasets; NDA 217188.
Subjects with no symptom data or no viral RNA data were not included in the analyses.
[a] Percentage over total subjects.
[b] Percentage over those who achieved combined recovery.
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in treatment arm

Discussion

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

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

Overall, these findings indicate that in a subset of SARS-CoV-2 infections, virologic and/or symptomatic rebound may occur as part of the natural progression and resolution of COVID-19 disease, irrespective of PAXLOVID treatment. Two ongoing clinical trials of PAXLOVID will further characterize the frequency of COVID-19 rebound following different durations of PAXLOVID treatment in immunocompromised subjects (EPIC-IC, NCT05438602) and the potential benefit of PAXLOVID retreatment in subjects with evidence of post-treatment COVID-19 rebound (C4671042, NCT05567952).

3.2 Safety Issues

- Serious adverse reactions due to DDIs.

3.2.1 Sources of Data for Safety

Safety data are derived from Phase 1, 2, and 3 trials, including the EPIC-HR, EPIC-SR, and EPIC-PEP trials where over 2400 subjects received the proposed PAXLOVID (nirmatrelvir 300 mg and ritonavir 100 mg) twice daily 5-day regimen. In addition, 911 subjects received PAXLOVID for 10 days in EPIC-PEP. Finally, postauthorization reports of AEs after PAXLOVID use were also reviewed to detect safety signals outside of the clinical trial setting.

3.2.2 Safety Summary

Clinical Trials

PAXLOVID demonstrated an overall favorable safety profile in the clinical trials (Table 11). The incidences of AEs were generally similar between treatment groups in EPIC-HR, EPIC-SR, and EPIC-PEP. The incidences of severe AEs, serious AEs, and AEs leading to permanent discontinuation of study drug were similar or higher in the placebo group compared to the PAXLOVID group. No deaths occurred in PAXLOVID-treated subjects.

Table 11. Overview of Adverse Events[a], Safety Population, Trials EPIC-HR[b], EPIC-SR[b], EPIC-PEP[c]

	EPIC-HR		EPIC-SR		EPIC-PEP		
	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Event Category							
SAE	18 (1.7)	71 (6.7)	8 (1.5)	11 (2.1)	3 (0.3)	1 (0.1)	2 (0.2)
SAEs with fatal outcome	0	13 (1.2)	0	1 (0.2)	0	0	0
Life-threatening SAEs	3 (0.3)	13 (1.2)	1 (0.2)	3 (0.6)	0	1 (0.1)	1 (0.1)
AE leading to permanent discontinuation of study drug	21 (2.0)	45 (4.3)	10 (1.9)	5 (0.9)	10 (1.1)	11 (1.2)	14 (1.6)
AE leading to dose modification of study drug	4 (0.4)	4 (0.4)	1 (0.2)	2 (0.4)	1 (0.1)	1 (0.1)	0
AE leading to interruption of study drug	4 (0.4)	4 (0.4)	1 (0.2)	2 (0.4)	1 (0.1)	1 (0.1)	0
Any AE[d]	228 (22.0)	256 (24.3)	126 (23.3)	126 (23.9)	218 (23.9)	212 (23.3)	195 (21.7)
Severe and worse	42 (4.0)	103 (9.8)	18 (3.3)	22 (4.2)	26 (2.9)	12 (1.3)	16 (1.8)
Moderate	68 (6.6)	71 (6.7)	34 (6.3)	35 (6.6)	63 (6.9)	63 (6.9)	60 (6.7)
Mild	118 (11.4)	82 (7.8)	74 (13.7)	69 (13.1)	129 (14.1)	137 (15.0)	119 (13.3)

Source: adae.xpt; software, R; NDA 217188.

[a] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit for EPIC-HR and EPIC-SR and prior to Day 38 visit for EPIC-PEP.

[b] Duration of treatment is 5 days.

[c] Duration of treatment is 5 or 10 days.

[d] Severity as assessed by the investigator.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Common treatment-emergent AEs observed in EPIC-HR, EPIC-SR, and EPIC-PEP are shown in Table 12. The most common treatment-emergent AEs (≥2% incidence) in the EPIC-HR PAXLOVID group were dysgeusia and diarrhea, and these occurred at a higher frequency compared to the placebo group (4.6% and 3.0% versus 0.1% and 1.5%, respectively). The most common treatment-emergent AEs observed in EPIC-SR and EPIC-PEP were consistent with those observed in EPIC-HR.

The most common serious AEs (≥2 subjects) in EPIC-HR PAXLOVID-treated subjects were COVID-19-related (COVID-19 0.2%; COVID-19 pneumonia 0.7%) and occurred at a lower frequency than in placebo-treated subjects (COVID-19 0.7%; COVID-19 pneumonia 3.4%). The most common discontinuations due to AEs (≥2 subjects) in EPIC-HR PAXLOVID-treated subjects were nausea (0.5%), vomiting (0.4%), dysgeusia (0.2%), creatinine renal clearance decreased (0.2%), GFR decreased (0.2%), and white blood cell count decreased (0.2%), and discontinuations due to AEs occurred at a similar frequency in placebo-treated subjects (nausea 0.5%; vomiting 0.2%; dysgeusia 0%; creatinine renal clearance decreased 0.4%; GFR decreased 0.2%; white blood cell count decreased 0%). Reported serious AEs and discontinuations due to AEs observed in EPIC-SR and EPIC-PEP were consistent with those observed in EPIC-HR.

Prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID. In the EPIC-PEP trial, similar safety profiles were observed in the PAXLOVID 5-day and 10-day treatment groups.

Table 12. Subjects With Common Adverse Events[a] Occurring at ≥1% Frequency, Safety Population, Trials EPIC-HR[b], EPIC-SR[b], and EPIC-PEP[c]

	EPIC-HR		EPIC-SR		EPIC-PEP		
Preferred Term	PAXLOVID N=1038 n (%)	Placebo N=1053 n (%)	PAXLOVID N=540 n (%)	Placebo N=528 n (%)	PAXLOVID 5 Days N=912 n (%)	PAXLOVID 10 Days N=911 n (%)	Placebo N=898 n (%)
Any AE	228 (22.0)	256 (24.3)	126 (23.3)	126 (23.9)	218 (23.9)	212 (23.3)	195 (21.7)
Dysgeusia	48 (4.6)	1 (0.1)	30 (5.6)	2 (0.4)	54 (5.9)	62 (6.8)	6 (0.7)
Diarrhea	31 (3.0)	16 (1.5)	22 (4.1)	16 (3.0)	23 (2.5)	22 (2.4)	15 (1.7)
Fibrin D dimer increased	22 (2.1)	30 (2.8)	6 (1.1)	6 (1.1)	18 (2.0)	13 (1.4)	4 (0.4)
Alanine aminotransferase increased	17 (1.6)	27 (2.6)	13 (2.4)	8 (1.5)	2 (0.2)	6 (0.7)	11 (1.2)
Nausea	15 (1.4)	19 (1.8)	17 (3.1)	16 (3.0)	16 (1.8)	12 (1.3)	14 (1.6)
Creatinine renal clearance decreased	14 (1.3)	16 (1.5)	5 (0.9)	4 (0.8)	9 (1.0)	5 (0.5)	5 (0.6)
Headache	12 (1.2)	13 (1.2)	6 (1.1)	6 (1.1)	15 (1.6)	17 (1.9)	29 (3.2)
Vomiting	12 (1.2)	9 (0.9)	10 (1.9)	11 (2.1)	7 (0.8)	3 (0.3)	3 (0.3)
Aspartate aminotransferase increased	10 (1.0)	14 (1.3)	7 (1.3)	4 (0.8)	2 (0.2)	5 (0.5)	7 (0.8)
C-reactive protein increased	10 (1.0)	13 (1.2)	3 (0.6)	2 (0.4)	0	1 (0.1)	4 (0.4)
Activated partial thromboplastin time prolonged	9 (0.9)	12 (1.1)	3 (0.6)	6 (1.1)	11 (1.2)	14 (1.5)	22 (2.4)
COVID-19 pneumonia	8 (0.8)	40 (3.8)	4 (0.7)	10 (1.9)	2 (0.2)	1 (0.1)	1 (0.1)
Cough	6 (0.6)	6 (0.6)	0	1 (0.2)	10 (1.1)	2 (0.2)	12 (1.3)
Blood thyroid stimulating hormone increased	5 (0.5)	7 (0.7)	2 (0.4)	5 (0.9)	11 (1.2)	8 (0.9)	10 (1.1)
Nasal congestion	4 (0.4)	0	0	0	4 (0.4)	3 (0.3)	10 (1.1)
COVID-19	3 (0.3)	13 (1.2)	0	1 (0.2)	27 (3.0)	26 (2.9)	36 (4.0)
Asthenia	3 (0.3)	3 (0.3)	2 (0.4)	2 (0.4)	10 (1.1)	7 (0.8)	17 (1.9)
Pneumonia	2 (0.2)	15 (1.4)	2 (0.4)	5 (0.9)	0	1 (0.1)	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)	5 (0.5)	4 (0.7)	4 (0.8)	12 (1.3)	15 (1.6)	13 (1.4)
Nasopharyngitis	1 (0.1)	0	1 (0.2)	1 (0.2)	13 (1.4)	9 (1.0)	6 (0.7)
Upper respiratory tract infection	1 (0.1)	0	0	0	20 (2.2)	17 (1.9)	18 (2.0)

Source: adae.xpt; software, R; NDA 217188.

[a] Treatment-emergent adverse events defined as adverse events started on the administration of study drugs and prior to Day 34 visit for EPIC-HR and EPIC-SR and prior to Day 38 visit for EPIC-PEP.

[b] Duration of treatment is 5 days.

[c] Duration of treatment is 5 or 10 days.

Coded as Medical Dictionary for Regulatory Activities preferred terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event

Safety Surveillance Under EUA

Over 11 million patients worldwide have received PAXLOVID for the treatment of COVID-19 since it was first authorized for emergency use in December 2021, including over 8 million patients in the United States. AEs following use of PAXLOVID that were reported to the FDA Adverse Events Reporting System, the FDA American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium Pharmacovigilance Project Subregistry, and the medical literature have been reviewed regularly by the Office of Surveillance and Epidemiology (OSE) to detect new safety signals. The following adverse reactions have been identified by OSE or the Applicant to date during use of PAXLOVID under EUA:

- Immune System Disorders: Anaphylaxis and other hypersensitivity reactions
  - In addition, cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of PAXLOVID.
- Nervous System Disorders: Headache
- Vascular Disorders: Hypertension
- Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
- General Disorders and Administration Site Conditions: Malaise

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions due to DDIs between PAXLOVID and concomitant medications have also been reported; these are described in detail below.

3.2.3 Safety Issues in Detail

Serious Adverse Reactions Due to DDIs

Background

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

Ritonavir exhibits near-maximal CYP3A inhibition when administered at a dose of 100 mg and can result in significant elevations of concomitant medications that are metabolized by the CYP3A isoenzyme. In the current PAXLOVID EUA Fact Sheet for Healthcare Providers, the table of "Established and Other Potentially Significant Drug Interactions" currently lists 143 drugs that have DDIs with PAXLOVID, as well as a statement that the listed drugs are not considered a comprehensive list. The 143 listed drugs include 37 drugs that are contraindicated with PAXLOVID, 21 drugs for which the recommendation is "avoid concomitant use" or "discontinue use prior to initiation of PAXLOVID", 49 drugs for which a dose adjustment is recommended or suggested, and 6 drugs for which therapeutic drug concentration or pharmacodynamic laboratory marker monitoring is recommended. The contraindications and drug-drug interactions included in the PAXLOVID EUA Fact Sheet for Healthcare Providers mirror those in the

Norvir and HIV boosted protease inhibitor labels with several additions from the National Institutes of Health guidelines for DDIs with PAXLOVID. Of note, drugs that are not contraindicated or listed as "avoid concomitant use" can still lead to clinically significant DDIs if not appropriately managed, such as renal failure (tacrolimus) or fatal respiratory depression (some narcotic analgesics).

Assessment

Analysis of Available Data

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

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

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

The PAXLOVID-eligible population, i.e., adults who are at high risk for development of severe COVID-19, are likely to be taking concomitant medications that have DDIs with PAXLOVID. Analyses were performed using the Medicare database from December 22, 2021 to September 10, 2022 and the Veterans Affairs (VA) database from January 01, 2022 to October 31, 2022, among adults who had COVID-19 and were eligible for PAXLOVID treatment based on being high risk for severe COVID-19 (due to age ≥65 years or high-risk comorbidities[8]) and not having evidence of severe renal or hepatic impairment. Drugs included in the August 25, 2022 update to the PAXLOVID Fact Sheet for Healthcare Providers were used to determine drugs with PAXLOVID DDIs.

In the Medicare and VA databases, respectively, 67% and 65% of PAXLOVID-eligible adults were on a drug with any DDI with PAXLOVID at the time of COVID-19 diagnosis, including 12% and 9% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 39% and 40% on a drug for which the PAXLOVID fact sheet recommended "avoid concomitant use", and 43% and 47% on a drug with other risk of DDI with PAXLOVID (not contraindicated nor listed as "avoid concomitant use"). A similar analysis was performed in the VA database with a broader definition of high risk for severe COVID-19 (age ≥50 years or high-risk comorbidities); in this analysis, 57% of eligible adults were on a drug with any DDI with PAXLOVID at the time of COVID-19 diagnosis, including 8% on a drug contraindicated with PAXLOVID at the time of COVID-19 diagnosis, 34% on a drug for which the PAXLOVID fact sheet

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

recommended “avoid concomitant use”, and 41% on a drug with other risk of DDI with PAXLOVID (not contraindicated nor listed as “avoid concomitant use”).

In all the analyses, the most common drugs with DDIs being taken by PAXLOVID-eligible adults were atorvastatin and amlodipine, and almost all of the 10 most common DDI drugs from each of the analyses could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring (depending on the clinical situation for each particular patient). One limitation of these analyses is that the Medicare and VA populations may not fully represent the overall PAXLOVID-eligible U.S. population; with a few exceptions, adults must be ≥65 years of age to be eligible for Medicare, and the VA population is disproportionately male. However, despite these limitations, these analyses indicate that a sizeable proportion of PAXLOVID-eligible adults are taking medications that have DDIs with PAXLOVID.

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

PAXLOVID is prescribed by a broad range of healthcare providers who may not be familiar with ritonavir DDIs. An OSE analysis was performed using the Symphony Health Metys™ drug utilization database which provides dispensed prescription estimates from a sample of U.S. outpatient pharmacies, representing ~85% of all retail prescriptions, 73% of all mail-order prescriptions, 75% of all specialty prescriptions, and 50% of all long-term care prescriptions, with prescription estimates projected to the national level. From December 25, 2021 to January 13, 2023, most PAXLOVID prescriptions in the United States were from adult primary care practitioners (74% from family medicine, general medicine, or internal medicine) or emergency room practitioners (7%), see Section 5.2.[9] In contrast, other ritonavir-containing products that are used to treat HIV or hepatitis C virus are generally prescribed by HIV or hepatitis specialists who may be more experienced with managing ritonavir DDIs.

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

OSE analyzed cases of adverse events following use of PAXLOVID for the treatment of COVID-19 under EUA that were reported to the FDA Adverse Events Reporting System, the FACT Pharmacovigilance Project Subregistry, and the medical literature through January 30, 2023[10]. OSE identified 301 cases of AEs that they assessed as possibly or probably related to DDIs included in the Fact Sheet for Healthcare Providers. A total of 271 of these cases reported at least one serious outcome, including 147 reporting hospitalization. Six cases reported a fatal outcome after a DDI-related AE (four related to concomitant tacrolimus use, one related to concomitant verapamil use, and one related to concomitant use of both nifedipine and atorvastatin). Despite mandatory AE reporting requirements, FDA is aware that not all AEs associated with PAXLOVID were reported; therefore, the incidences of these events cannot be calculated based on these data.

[9] Source: Symphony Health Metys™. Week ending December 31, 2021 to week ending January 13, 2023. Data extracted January 2023.

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

Benefit-Risk Considerations

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

This risk reduction in the COVID-19 vaccinated or SARS-CoV-2 seropositive high-risk population remains a large benefit on a population level. There were approximately 4000 COVID-19-related deaths and 35,000 COVID-19-related hospitalizations each week in the United States in January 2023 (CDC 2020a); consequently, even with a conservative estimate of benefit (25% of PAXLOVID-eligible patients unable to take PAXLOVID due to DDIs and an RRR of 50%), PAXLOVID could still lead to 1500 lives saved and 13,000 hospitalizations averted each week in the United States.

However, on an individual patient level, with an absolute risk reduction with PAXLOVID for the hospitalization/death endpoint of about 1 to 2% for a patient with baseline SARS-CoV-2 immunity, individual patients could have DDIs associated with risks that could outweigh this benefit, particularly if the DDIs are not adequately managed. Whether or not the DDIs can be managed such that PAXLOVID would have a favorable benefit-risk assessment varies both by the specific medication and by the individual patient. Some of the medications that are either contraindicated or have a recommendation of “avoid concomitant use” with PAXLOVID cannot be safely held, such that PAXLOVID would not be an appropriate choice. For other medications, the DDIs could be managed by temporarily holding the medication (e.g., atorvastatin), adjusting the dose of the concomitant medication, close laboratory monitoring, and/or monitoring for adverse events. In addition, prescribers should also consider patient factors, such as a patient’s ability to comply with instructions for dose adjustment or monitoring, the patient’s estimated risk for development of severe COVID-19, and the patient’s risk from the particular adverse reaction associated with the DDI, when deciding whether to prescribe PAXLOVID to their individual patient with risk of DDIs.

Conclusion

Serious adverse reactions due to DDIs are the key safety concern with PAXLOVID. Safety surveillance data under EUA indicate that many PAXLOVID-eligible patients are on medications with DDIs with PAXLOVID (though the most common medications with DDIs could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring), that the majority of PAXLOVID prescribers are adult primary care practitioners (who may not be experienced in managing ritonavir DDIs), and that serious adverse reactions, including death, have been reported in association with DDIs that are included in the current EUA Fact Sheet for Healthcare Providers. In order to safely prescribe PAXLOVID, the potential for DDIs needs to be considered by all prescribers, both to take actions to manage DDIs and also to determine whether PAXLOVID is an appropriate treatment choice for each individual patient when factoring in the risks of serious adverse reactions due to DDIs.

Risk Mitigation

No major safety concerns were identified in EPIC-HR, EPIC-SR, and EPIC-PEP. The risk of serious adverse reactions due to DDIs will be described appropriately in labeling, should PAXLOVID receive marketing approval, to ensure that prescribers are aware of this risk.

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5 Appendix

5.1 Literature Review on PAXLOVID Effectiveness RWE

Review Methods and Materials

The Division of Epidemiology II searched the WHO COVID-19-research database and PubMed, using the search terms "Paxlovid" and "epidemiology/RWE study"(Section 5.1.1). We excluded articles that:

- Did not report a study that evaluated PAXLOVID effectiveness.
- Did not report observational studies (e.g., clinical trials, case reports, case series).
- Did not report findings of analyses on PAXLOVID effectiveness, compared to non-PAXLOVID-treated COVID-19 patients.
- Did not evaluate PAXLOVID effectiveness in an outpatient COVID-19 population.

We further applied the following criteria for selecting studies for in-depth review:

- Studies that fulfilled the following key data sources and design features:
  - **Longitudinal data**: used data source(s) that allows longitudinal capture of the key covariates across different healthcare settings:
    - Diagnosis/test of COVID-19 in an ambulatory setting.
    - Exposure to PAXLOVID as outpatient treatment.
    - Vaccination status prior to COVID-19 diagnosis/PAXLOVID exposure.
    - Clinical outcome (hospitalization or death) after COVID-19 diagnosis/PAXLOVID exposure.
    - Comorbid conditions and concurrent medication use at time of COVID-19 diagnosis/PAXLOVID use.
  - **"Nonuser" reference group**: Included "nonuser" as a reference group, since we do not have trial data to support effectiveness of PAXLOVID against an "active control" (i.e., other potential COVID-19 treatments).
  - **Index time selection**: Applied design feature that can account for the potential bias introduced by "index time" selection for the treated and untreated patients, given that PAXLOVID users were COVID-19 patients who remained hospitalization-free and survived from diagnosis to treatment, which can lead to bias in favor of finding PAXLOVID effectiveness.

Review Results

Our last literature search was conducted on January 30, 2023. Among the 297 English-language articles identified by our search terms, 22 were observational studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations (Section 5.1.1); we excluded:

- Three publications (Najjar-Debbiny et al. 2023; Wai et al. 2023; Yip et al. 2023) of shorter study duration that used the same data source as another identified publication[11].

[11] The publication by Najjar-Debbiny et al. was excluded due to an overlapping Israeli data source with Arbel et al. The publications by Yip et al. and Wai et al. were based on the same territory-wide population in Hong Kong as that by Wong et al.

- One publication (Xie et al.) that described a study that only evaluated "post-acute sequelae of COVID-19"[12] occurring from 30 to 90 days after SARS-CoV-2 infection, due to significant design concerns:
  - The validity of code-based algorithms to capture the individual post-acute COVID-19 sequelae were not reported in the article.
  - Important confounders (e.g., use of certain medications that could influence the risk of the individual clinical condition that consists of "post-acute COVID-19 sequelae") were neither reported nor accounted for in the analyses.

We screened the remaining publications and further excluded 13 studies that did not meet all the key data source and design features criteria for in-depth review (Table 13).

Table 13. Screening of the Identified Observational RWE Studies on Outpatient PAXLOVID Effectiveness

		Fulfilled Key Data Source and Design Features for In-Depth Review		
	Study Screened	**Longitudinal Data Source**	**Nonuser Reference Group**	**Design to Handle Bias Due to Index Time Selection**
Excluded	Hedvat et al. (2022)	**No**	Yes	**No**
	Dryden-Peterson et al. (2023)	**No**	Yes	Yes
	Ganatra et al. (2022)	**No**	Yes	**No**
	Zhou et al.	**No**	Yes	Yes
	Aggarwal et al.	**No**	Yes	**No**
	Bruno et al. (2022a)	**Unclear**	**No**	N/A
	Bruno et al. (2022b)	**Unclear**	**No**	N/A
	Gentile et al. (2022)	**Unclear**	**No**	N/A
	Park et al. (2022a)	Yes	Yes	**No**
	Park et al. (2022b)	Yes	Yes	**No**
	Qian et al. (2022)	**No**	Yes	**No**
	Shah et al. (2022)	**No**	Yes	**Unclear**
	Tiseo et al. (2023)	**Unclear**	**No**	N/A
Included	Arbel et al. (2022)	Yes	Yes	Yes
	Wong et al. (2022a)	Yes	Yes	Yes
	Bajema et al. (2022)	Yes	Yes	Yes
	Schwartz et al. (2022)	Yes	Yes	Yes
	Lewnard et al. (2023)	Yes	Yes	Yes

Source: Literature review.
Abbreviations: N/A, not applicable; RWE, real-world-evidence

[12] Post-acute death or hospitalization and individual sequela including ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough.

Five studies were included in our in-depth review (Arbel, Wong, Bajema, Schwartz, and Lewnard). Of note, the publications by Bajema, Schwartz, and Lewnard are non-peer-reviewed preprints.[13]

Briefly, the five reviewed studies were cohort studies involving nonhospitalized patients with positive SARS-CoV-2 RT-PCR or antigen test results during the period of Omicron-variant dominance. Two of the studies used nation-wide or territory-wide electronic health records of hospitals and outpatient clinics, one in Israel and one in China (Hong Kong); one study used a province-wide integrated health-care data from Quebec, Canada; two studies used electronic health records and administrative claims data from the U.S. Veterans Health Administration and an integrated healthcare system of a single U.S. state. They also included broader study populations than those included in the pivotal trials—with respect to age, underlying high-risk comorbidities, and COVID-19 vaccination status.

All studies evaluated the risk of COVID-19-related hospitalization or all-cause hospitalization in PAXLOVID-treated COVID-19 patients compared to those not treated with PAXLOVID (nonusers). Some studies also evaluated other clinical outcomes, such as mortality or in-hospital COVID-19 progression. The RWE studies in general reported PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status.

Conclusions on the Quality of the Available PAXLOVID RWE Studies

Seventeen of the twenty-two identified RWE studies reporting effectiveness of outpatient PAXLOVID use were excluded from in-depth review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources, and/or were unable to account for potential bias introduced by index time selection. The five remaining studies consistently reported that PAXLOVID use was associated with a reduced risk of worsening COVID-19 outcomes in broader populations than included in the pivotal trials—with respect to age, underlying "high-risk" comorbidities, and COVID-19 vaccination status in the Omicron era.

The information available for the reviewed observational studies was insufficient to determine their quality.

Details on the Assessment of the Eligible Paxlovid RWE Studies That Informed the Conclusions

Compared to the studies excluded from in-depth review, the five reviewed studies used more appropriate data sources, study design, or analytical approaches to account for the potential bias introduced by index time selection.

However, unlike Applicant-sponsored efficacy trials that provide more information to assess study quality, none of the reviewed RWE studies published their protocol and analytical plan prior to the final study report. In at least one study (Lewnard), the analyses and results differed notably between two version of the preprints. So, it was difficult to track whether these studies were conducted according to a prespecified protocol and analytical plan. Additionally, patient-level data on the observational studies were unavailable to verify the correct implementation of study design and statistical methods, which is a standard review process for trial data that are used to support treatment efficacy.

[13] The manuscripts are available as preprints; i.e., they have not been peer-reviewed. Non-peer-reviewed preprints may not be accepted for publication by a peer-reviewed journal. If they are formally published in a peer-reviewed journal, there may be revisions of the methods or analyses to address the editor's or reviewers' comments.

Despite insufficient information on studies due to what is reported in the public domain, we still identified methodological or analytical issues in the reviewed studies. Some of these issues had reasonably predictable impact on the study findings, while there were other review issues for which we would need more information than was provided to determine the potential impact on the study results. These issues are summarized below.

Review Issues With a Reasonably Predictable Impact on Study Findings

Residual Confounding by COVID-19 Severity (All Studies)

Three of the reviewed studies did not capture or adjust for baseline COVID-19 severity (Arbel, Wong, and Schwartz). The studies by Bajema and Lewnard accounted for the presence of COVID-19 symptoms at baseline; however, the validity of the operational definitions for COVID-19 symptoms was not reported. Residual confounding due to COVID-19 severity would likely underestimate PAXLOVID effectiveness, given that PAXLOVID was more likely to be given to symptomatic patients or patients with severe symptoms.

Residual Confounding by High-Risk Comorbidities (Arbel and Wong Studies)

Although the Arbel study captured information on medical conditions that increase a patient's risk for COVID-19 progression (high-risk comorbidities), not all were adjusted for in the analyses. The Wong study matched the treated and non-treated patients on a summary comorbidity risk score (i.e., Charlson Comorbidity Index), which did not guarantee the component medical conditions of the risk score would be balanced between treatment groups. Furthermore, the component medical conditions of the Charlson Comorbidity Index were not an exact match to the high-risk comorbidities for worse COVID-19 progression. For example, the Charlson Comorbidity Index does not account for all immunosuppressive diseases (e.g., bone marrow or organ transplantation), prolonged use of immune-weakening medications, chronic lung diseases (except for chronic obstructive pulmonary disease), neurodevelopmental disorders, sickle cell disease. Lastly, the Wong study did not report distribution of high-risk comorbidities for COVID-19 progression to inform if these important confounders were balanced between treatment groups.

Residual confounding due to unbalanced high-risk comorbidities would likely bias the risk estimate towards the null (underestimate of PAXLOVID effectiveness), given that PAXLOVID treatment for COVID-19 patients with high-risk comorbidities was likely prioritized.

Outcome Selection (Bajema and Lewnard Studies)

Studies by Bajema and Lewnard used "all-cause hospitalization or death" as the primary outcome, which included events that are unrelated to PAXLOVID effect (i.e., hospitalization or death due to causes other than COVID-19). If the proportion of outcome events unrelated to COVID-19 is nondifferential between treated and nontreated groups, it would bias findings toward null (underestimate of PAXLOVID effectiveness). The proportion of events unrelated to COVID-19 can be higher among PAXLOVID users, given that administration of PAXLOVID is prioritized to patients with comorbidities that may lead to a higher risk of hospitalization or death due to non-COVID-19 causes, which will also lead to underestimate of PAXLOVID effectiveness.

Study Power to Evaluate PAXLOVID Effectiveness in Subgroups (All Studies)

Only one reviewed study reported a priori power analyses (Bajema et al.). All the reviewed studies were not powered to formally test treatment effect modification by patient characteristics, or to evaluate PAXLOVID effectiveness in any patient subgroup. Some studies suggested that PAXLOVID effectiveness may differ by age, for example, Arbel concluded that "no evidence of benefit was found in patients younger than 65 years of age." The study findings did not support a statistically significant reduction in COVID-19 hospitalization risk (hazard ratio=0.74, 95% CI=0.35 to 1.58) or death (hazard ratio=1.32, 95% CI=0.16 to 10.75) associated with PAXLOVID use among a younger population (40 to 65 years of age). However, it is likely that the study did not have sufficient power to evaluate PAXLOVID effectiveness in the younger population, evidenced by the wide 95% CIs of the effect estimates.

Review Issues That Require More Information to Evaluate the Impact on Study Results

Unvalidated Outcome Measures

COVID-19-Related Hospitalization (Arbel, Wong, and Schwartz Studies)

Three reviewed studies included "hospitalization due to COVID-19" as the endpoint, or part of the endpoints (Arbel, Wong, and Schwartz). However, none of the studies provided data to support the validity of the measure for "COVID-related hospitalization." Without a better understanding of how information on COVID-19 related hospitalization was recorded or derived, it is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Post-COVID-19 Conditions (Bajema Study)

The Bajema study also evaluated PAXLOVID's effectiveness on multiple potential post-COVID-19 conditions;[14] however, they did not provide data to support the International Classification of Diseases, 10th Edition diagnosis codes that were used to capture these conditions. It is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Residual Confounding by Other Potential Confounders

Information on the frequencies and the distribution of the potential confounders (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

[14] Post-COVID-19 conditions in the Bajema study comprise: acute coronary syndrome, cardiac dysrhythmias, cardiovascular disease, chest pain, heart failure and cardiomyopathy, hypertension, myocarditis, respiratory symptoms (shortness of breath/dyspnea, any respiratory distress/failure, any bronchitis, hypoxemia, bronchiectasis, any non-COVID-19 pneumonia including influenza, cough, wheezing, sneezing, nasal congestion/sinusitis, sore throat, pharyngitis, laryngitis, tonsillitis), asthma, COPD and emphysema, obstructive sleep apnea or obesity hypoventilation, renal conditions (acute kidney injury, chronic kidney disease, dialysis), venous thromboembolism, pulmonary embolism, abdominal pain, esophageal disorders, gastrointestinal disorders, cerebrovascular disease, dementia, smell and taste disturbance, headache, sleeping disorders, other neurologic conditions (peripheral nerve disorders [i.e., neuropathy, Guillain-Barre syndrome], epilepsy, multiple sclerosis, complex regional pain syndrome, Parkinson disease), depression, other mood disorders (bipolar, schizophrenia, psychosis), anxiety, PTSD, substance-related disorder, musculoskeletal conditions (any myositis, muscle wasting and atrophy, contracture of muscle, myalgias), diabetes, disorders of lipid metabolism, obesity, malaise and fatigue

Detailed Information on COVID-19 Vaccination (Arbel, Wong, and Lewnard Studies)

Total dose, timing of last dose, type or manufacturer of the COVID-19 vaccine could impact PAXLOVID effectiveness for COVID-19 outcomes. Not all reviewed studies captured or accounted for detailed information on COVID-19 vaccination in their analyses. The Arbel and Wong studies only reported and accounted for vaccination status as dichotomous variables ("presence of prior immunity or not" in Arbel study, "fully vaccinated or not" in the Wong study). The Lewnard study only adjusted for the number of total vaccine doses received in their analyses.

Other Outpatient COVID-19 Medication Use at Baseline (Lewnard Study)

Prior or concurrent use of other outpatient medications for COVID-19 at baseline can be a potential confounder as they can influence COVID-19-related clinical outcomes. The Lewnard study did not exclude patients who used other COVID-19 medications at baseline, while several treatment options were available in the United States during the timeframe of the study. The study also did not report the use of the other outpatient COVID-19 treatment at baseline, nor adjusted for baseline use of these medications in their analyses.

Other Medications Use (Bajema Study)

The Bajema study included analyses of PAXLOVID effectiveness on risk of long-term outcomes (i.e. hospital admission, nursing skilled nursing home facility admission, all-cause death, or post-COVID-19 conditions) that occurred 31 to 180 days after diagnosis. PAXLOVID was prioritized for patients with COVID-19 and certain comorbidities that are also components of the "post-COVID conditions"; for example, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, diabetes, obesity. The use of other medications, especially those that are indicated for the components of the post-COVID-19 conditions, are important confounders that were not reported, nor accounted for in the study.

Handling of Post-index Time COVID-19 Treatment

Information on the frequencies and the distribution of post-index time COVID-19 treatment changes (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Other Outpatient COVID-19 Medication Use (All Studies)

In the analyses of PAXLOVID's effectiveness on hospitalization, use of other outpatient COVID-19 medications during follow-up could be on the causal pathway between PAXLOVID use and COVID-19 outcome—the need to use another treatment can be an early indication that PAXLOVID did not work well in preventing disease progression. Use of other COVID-19 treatments also have an impact on COVID-19 outcome, independently from PAXLOVID's effectiveness.

Use of other outpatient COVID-19 medications was a censor criterion in the Wong study, but not in the Lewnard or Bajema studies, while the Arbel and Schwartz studies did not clearly state how they handled patients who initiated another outpatient COVID-19 treatment during follow-up. If the use of other outpatient COVID-19 medication is uncommon, these different approaches would likely all be acceptable; however, none of the three reviewed studies reported the extent of other COVID-19 medications used during follow-up.

Inpatient Medical Management (Arbel, Wong, Bajema, and Lewnard Studies)

Four of the reviewed studies (Arbel, Wong, Bajema, and Lewnard) also evaluated outpatient PAXLOVID's impact on in-patient outcomes, such as in-hospital disease progression, invasive mechanical ventilation use, intensive care unit admission and death, or post-acute COVID-19 symptoms. In these analyses, the medical treatment that patients received during hospitalization, such as inpatient COVID-19 treatment, could be on the causal pathway. None of these studies reported information on inpatient medical management during follow-up, nor accounted for its impact in the analyses.

Concern on Statistical Methods

Ambiguous Statistical Methods and Results (Lewnard Study)

The details of the analyses and the results are not clear. Without knowledge of the details, some of the results are difficult to review and interpret. The definition of the discordant pairs in the results tables (Table 2 and Table 3) is not clear and the summaries of the discordant pairs do not seem to align with the effectiveness estimates. It is also unclear whether immortal time in treated subjects is handled properly when determining discordant pairs. In addition, a large number of the eligible patients were not included in the analyses, calling into question the generalizability of the results.

Handling of Immortal Time Bias (Schwartz and Wong Studies)

The Schwartz study assigned random index dates to the unexposed group based on the time-to-dispense distribution from the exposed group. This approach did not consider factors that may impact the dispensing time for each subject (e.g., the presence of symptoms) and may not fully fix the immortal time bias problem.

The primary analyses of the Wong study set the index time at COVID-19 symptom onset or diagnosis, which introduced immortal time in the PAXLOVID-treated group and could overestimate PAXLOVID effectiveness. The investigators conducted post hoc sensitivity analyses that treated exposure status as a "time-varying" variable to account for immortal time bias. The findings of this sensitivity analysis that accounted for immortal time bias consistently support PAXLOVID effectiveness as the primary analyses in the overall study population. It is unclear if the conclusion would be the same for the subgroup analyses stratified by vaccination status, as the author did not report the findings of the sensitivity analyses by patient subgroup.

Handling of Missing Data (All Studies)

All the studies except for the Lewnard study did not report the degree of missing data for important baseline covariates. Most of the studies did not specify a method of handling missing data other than excluding subjects with missing covariates.

5.1.1 RWE Literature Search Process (Steps and Numbers of Articles Remaining)

1. English language article with “Paxlovid OR nirmatrelvir” AND keywords of “epidemiology or RWE study,” excluding animal, cellular, pharmacokinetic/pharmacodynamics, identified **297** articles (search terms are required in Title, Abstract, or Subject).
    a. Restrict to studies evaluating PAXLOVID effectiveness 44
    b. Exclude duplicate publications 26
    c. Exclude studies involving hospitalized subjects with COVID-19 22

RWE Literature Search Terms

Key Words for Epidemiology or RWE Studies

epidemiology OR observational OR non-randomized OR cohort OR sample OR adjustment OR "propensity score" OR "inverse probability weighting" OR "integrated health care system" OR multivariate OR multivariable OR population-based OR case-control OR database OR bayesian OR abstracted OR "convenience sample" OR "electronic health record" OR "systematic review" OR cohort OR case-control OR database OR datalink OR "claims data" OR "drug utilization" OR "electronic health records" OR "electronic medical records" OR biobank OR "pooled analysis" OR crossover OR registry OR registries OR meta-analysis OR retrospective OR prospective OR "cross sectional" OR cross-sectional OR "prevalence study" OR "longitudinal study" OR "before-after study" OR "administrative database" OR "insurance claim" OR matched-cohort OR population-based OR "insurance database" OR "claims database" OR "pharmaceutical claims" OR "case control" OR "meta analysis" OR self-controlled OR "self controlled" OR comparative OR emr OR prevalence OR incidence OR rate OR "administrative claim" OR “Real-World” OR “Real World” OR “RWE”.

Key Words for Animal, Cellular, and Pharmacokinetic/Pharmacodynamics Studies (for exclusion)

animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosophila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail

OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR atlantic cod OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR polymorphism OR plant OR pharmacokinetics OR pharmacokinetic OR pharmacodynamic OR pharmacodynamics.

5.2 Drug Utilization Database Description

Symphony Health Metys™

Powered by IDV® Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting its breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent ~85% of all U.S. retail prescriptions, 73% of all U.S. mail order prescriptions, 75% of all U.S. specialty prescriptions, and 50% of all U.S. long-term care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures ~96% of pharmaceutical distribution into nonretail outlets in the United States. The nonretail data are not projected to the national level. Metys™ Managed Markets metrics, such as rejections and reversals, are calculated using a 50% sample of pharmacy-adjudicated claims projected to the national level.