Introduction

New Drug Application (NDA) 217188
PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged

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

Antimicrobial Drugs Advisory Committee Meeting
March 16, 2023

John Farley, MD, MPH
Director, Office of Infectious Diseases
Center for Drug Evaluation and Research
Advisory Committee Meeting Purpose

The FDA is convening this Advisory Committee meeting to discuss whether the available data support an overall favorable benefit-risk assessment for the use of PAXLOVID for the treatment of mild-to-moderate COVID-19\(^1\) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.


Mild Illness: Individuals who have any of various signs and symptoms of COVID-19 but do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO\(_2\)) ≥94% on room air at sea level.
PAXLOVID

• Oral nirmatrelvir tablets co-packaged with ritonavir tablets
  – **Nirmatrelvir** is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M\text{pro}, also known as 3CL\text{pro} or nsp5), which is required for viral replication.
  – **Ritonavir** is an HIV-1 protease inhibitor and potent CYP3A inhibitor that is used to increase the plasma concentrations of nirmatrelvir.
    • Ritonavir itself is not active against SARS-CoV-2 M\text{pro}.

• **Proposed indication:** treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death

• **Dosage:** nirmatrelvir 300 mg + ritonavir 100 mg orally twice daily for 5 days
  – Moderate renal impairment (eGFR ≥ 30 to <60 mL/min): The proposed dosage is nirmatrelvir 150 mg + ritonavir 100 mg orally twice daily for 5 days.
The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death.
PAXLOVID – Drug Development Ongoing

• Our discussion today will not focus on pediatric use, as pediatric drug development is ongoing.

• Should this New Drug Application be approved, FDA anticipates that the EUA for PAXLOVID will remain in effect to continue authorizing treatment of adolescents with mild-moderate COVID-19 and further address other access needs.

• PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). Drug development for this population is ongoing.
Clinical Trials to be Discussed Today

- **EPIC-HR**: This trial 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. The trial was successful on its primary efficacy endpoint and demonstrated a reduction compared to placebo of COVID-19-related hospitalization or death from any cause.

- **EPIC-SR**: This trial 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.

- **EPIC-PEP**: This trial 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 prevention of symptomatic SARS-CoV-2 infection through Day 14.
Key Review Issues

- Efficacy of PAXLOVID in high-risk adults who are vaccinated against COVID-19 or had a prior SARS-CoV-2 infection
- Efficacy of PAXLOVID in the setting of the SARS-CoV-2 Omicron variant
- Impact of PAXLOVID on COVID-19 rebound
- Optimal duration of PAXLOVID treatment in immunocompromised patients
- Serious adverse reactions due to drug-drug interactions
Data Considerations

To inform the discussion of the key review issues:

• FDA will present subgroup analyses from EPIC-SR and EPIC-PEP. These trials failed on their primary endpoints. These analyses should be considered exploratory.

• FDA will present analyses of quantitative nasopharyngeal SARS-CoV-2 viral RNA shedding. FDA does not currently recommend SARS-CoV-2 virologic endpoints as primary endpoints in Phase 3 trials because there is currently no established predictive relationship between the magnitude and timing of viral shedding reductions and the extent of clinical benefit of how a patient feels, functions, or survives.

• Published real world evidence studies will likely be discussed. FDA has reviewed many of the these reports and found that the reports generally do not include sufficient information to allow for a complete review to determine their quality and assess for potential bias.
Voting Question

1. Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?
   a. If yes, please provide your rationale.
   b. If no, please provide your rationale and list what additional studies/trials are needed.
Discussion Questions

2. 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 Omicron subvariants.
   c. Individuals who are immunocompromised.

Please comment if additional data are needed in these populations.

Overview of the Day

- Applicant Presentations
- FDA Presentations
- Lunch
- Clarifying Questions
- Open Public Hearing
- Charge to the Committee
- Questions to the Committee/Committee Discussion
New Drug Application (NDA) 217188
PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged

Antimicrobial Drugs Advisory Committee Meeting
March 16, 2023

Division of Antivirals, Office of Infectious Diseases
Center for Drug Evaluation and Research
Overview

Glen Huang, DO, Clinical Reviewer
Advisory Committee Meeting Purpose

• The FDA is convening this Advisory Committee meeting to discuss whether the available data support an overall favorable benefit-risk assessment for the 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.
PAXLOVID

• Oral nirmatrelvir tablets co-packaged with ritonavir tablets
  – **Nirmatrelvir** is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M\text{pro}, also known as 3CL\text{pro} or nsp5), which is required for viral replication
  – **Ritonavir** is an HIV-1 protease inhibitor and potent CYP3A inhibitor that is used to increase the plasma concentrations of nirmatrelvir
    • Ritonavir itself is not active against SARS-CoV-2 M\text{pro}

• **Proposed indication:** treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death

• **Dosage:** nirmatrelvir 300 mg + ritonavir 100 mg orally twice daily for 5 days
  – Moderate renal impairment (eGFR ≥ 30 to <60 mL/min): the proposed dosage is nirmatrelvir 150 mg + ritonavir 100 mg orally twice daily for 5 days
PAXLOVID Emergency Use Authorization

• The FDA issued an EUA 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
  – EUA issuance supported by adult interim data from EPIC-HR in which PAXLOVID demonstrated reduced risk of COVID-19-related hospitalization or death from any cause through Day 28 when compared to placebo
Other Available COVID-19 Therapeutics in the U.S.

• **Remdesivir**: FDA-approved therapy administered intravenously for treatment of mild-to-moderate COVID-19 in non-hospitalized adults who are at high risk for progression to severe disease

• **Molnupiravir**: Oral therapy available under EUA for the treatment of adults with mild-to-moderate COVID-19 who are at high risk of progressing to severe disease and for whom alternative antiviral therapies are not accessible or clinically appropriate
# PAXLOVID Pivotal Trial

<table>
<thead>
<tr>
<th>Title</th>
<th>Design</th>
<th>Population</th>
<th>PAXLOVID Dose</th>
<th>Primary Endpoint</th>
<th>Time-Frame of Enrollment and Variants of Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal Trial</td>
<td>Phase 2/3, double blind, placebo-controlled (1:1) treatment trial</td>
<td>Unvaccinated adult outpatients with COVID-19 at high risk for severe disease (N=2113 subjects)</td>
<td>300/100 mg q12h x 5 days</td>
<td>Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28</td>
<td>July 2021 – November 2021 Variant of concern: Delta</td>
</tr>
</tbody>
</table>

**EPIC-HR**
# PAXLOVID Supportive Trials

<table>
<thead>
<tr>
<th>Title</th>
<th>Design</th>
<th>Population</th>
<th>PAXLOVID Dose</th>
<th>Primary Endpoint</th>
<th>Time-Frame of Enrollment and Variants of Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supportive Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPIC-SR</strong></td>
<td>Phase 2/3, double blind, placebo-controlled (1:1) treatment trial</td>
<td>Adult outpatients with COVID-19 who are fully vaccinated and have at least one risk factor for progression to severe disease or who are unvaccinated and have no risk factors for progression to severe disease (N=1075 subjects for interim 2021 analysis; N=221 for 2022 analysis)</td>
<td>300/100 mg q12h x 5 days</td>
<td>Time to sustained alleviation of all targeted signs/symptoms through Day 28</td>
<td>August 2021 – November 2021 (interim analysis) Variant of concern: Delta March 2022 – June 2022 (re-opened) Variant of concern: Omicron</td>
</tr>
<tr>
<td><strong>EPIC-PEP</strong></td>
<td>Phase 2/3, double blind, placebo-controlled (1:1:1) post-exposure prophylaxis trial</td>
<td>Asymptomatic adults with a negative screening SARS-CoV-2 rapid antigen test and who were exposed to household contacts who were symptomatic with confirmed COVID-19 (N=2736 subjects)</td>
<td>300/100 mg q12h x 5 days or 10 days</td>
<td>Proportion of subjects 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</td>
<td>September 2021 – March 2022 Variants of concern: Delta and Omicron</td>
</tr>
</tbody>
</table>
Key exclusion: previous SARS-CoV-2 infection or hospitalization for COVID-19 and prior receipt of convalescent COVID-19 plasma or COVID-19 vaccination

Concomitant medication: any medication or substances with clinically significant drug-drug interactions with PAXLOVID were prohibited during study treatment
EPIC-HR: Select Baseline Demographics/Characteristics

• 2113 unvaccinated subjects were randomized
• Most common risk factors
  – Body mass index ≥ 25 kg/m^2: 80%
  – Cigarette smoker: 39%
  – Hypertension: 32%
  – Age ≥ 60 years: 21%
• Immunosuppression: <1% (n=13)
• 49% of enrolled subjects had positive SARS-CoV-2 serology at baseline
  – Likely from prior unconfirmed or asymptomatic SARS-CoV-2 infections or early seroconversion to the current SARS-CoV-2 infection
### Pivotal Efficacy Data Supporting NDA

#### EPIC-HR Efficacy Results (mITT\(^a\))

<table>
<thead>
<tr>
<th>Primary endpoint(^b): COVID-19 related hospitalization or death from any cause through Day 28, n (%)</th>
<th>PAXLOVID (N=977)</th>
<th>Placebo (N=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (0.9%)</td>
<td>64 (6.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COVID-19 related hospitalization through Day 28, %</th>
<th>PAXLOVID (N=977)</th>
<th>Placebo (N=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (0.9%)</td>
<td>63 (6.4%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All-cause mortality through Day 28, %</th>
<th>PAXLOVID (N=977)</th>
<th>Placebo (N=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12 (1.2%)</td>
<td></td>
</tr>
</tbody>
</table>

---

a. Subjects dosed within 5 days of symptom onset who did not receive nor were expected to receive therapeutic mAb treatment

b. Determination of efficacy was based on interim analysis in mITT population (p-value<0.0001) using Kaplan-Meier estimates (subjects with no events were censored at the time of study discontinuation)

Abbreviations: mITT, modified intent-to-treat

- **EPIC-HR**: PAXLOVID versus placebo, for the primary endpoint:
  - Relative risk reduction (RRR): **86%** (95% confidence interval [CI]: 72-93%)
  - Absolute risk reduction (ARR): **5.6%** (95% CI: 4.0-7.3%)

- **EPIC-SR and EPIC-PEP**: did not meet their primary endpoints, but were used in the assessment of key review issues
## PAXLOVID Clinical Safety Database

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>No. of Subjects Who Received PAXLOVID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Safety Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC-HR</td>
<td>Unvaccinated adult outpatients with COVID-19 who are at high risk for progression to severe disease</td>
<td>5-day: 1038</td>
</tr>
<tr>
<td><strong>Supportive Safety Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC-SR</td>
<td>Adult outpatients with COVID-19 who are fully vaccinated and have at least one risk factor for progression to severe disease or who are unvaccinated and have no risk factors for progression to severe disease</td>
<td>5-day: 540</td>
</tr>
<tr>
<td>EPIC-PEP</td>
<td>Asymptomatic adults with a negative screening SARS-CoV-2 rapid antigen test and who were exposed to household contacts who were symptomatic with confirmed COVID-19</td>
<td>5-day: 912, 10-day: 911</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>3401&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>2490 subjects received 5-day duration of PAXLOVID

- **Post-authorization reports** of adverse events after PAXLOVID use were also reviewed to detect safety signals outside of the clinical trial setting.
Overview of Adverse Events in Clinical Trials

- PAXLOVID demonstrated an overall favorable safety profile in the clinical trials
- Both serious adverse events (SAE) and adverse events (AE) leading to discontinuation of study drug were infrequent (<5%) in the PAXLOVID arms of all three trials
- Most AEs were either mild or moderate in severity

<table>
<thead>
<tr>
<th>Event Category</th>
<th>EPIC-HR</th>
<th>EPIC-SR</th>
<th>EPIC-PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAXLOVID N=1038</td>
<td>Placebo N=1053</td>
<td>PAXLOVID N=540</td>
</tr>
<tr>
<td>SAE</td>
<td>18 (1.7)</td>
<td>71 (6.7)</td>
<td>8 (1.5)</td>
</tr>
<tr>
<td>AE leading to permanent discontinuation of study drug</td>
<td>21 (2.0)</td>
<td>45 (4.3)</td>
<td>10 (1.9)</td>
</tr>
<tr>
<td>Any AE</td>
<td>228 (22.0)</td>
<td>256 (24.3)</td>
<td>126 (23.3)</td>
</tr>
<tr>
<td>Severe and worse</td>
<td>42 (4.0)</td>
<td>103 (9.8)</td>
<td>18 (3.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>68 (6.6)</td>
<td>71 (6.7)</td>
<td>34 (6.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>118 (11.4)</td>
<td>82 (7.8)</td>
<td>74 (13.7)</td>
</tr>
</tbody>
</table>

Abbreviations: SAE, serious adverse event; AE, adverse event
**Common Adverse Events in PAXLOVID**

- **Dysgeusia** and **diarrhea** occurred at higher frequency in the PAXLOVID arms when compared to placebo in all three trials.
- Prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of PAXLOVID.

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>EPIC-HR</th>
<th></th>
<th></th>
<th>EPIC-SR</th>
<th></th>
<th></th>
<th>EPIC-PEP</th>
<th></th>
<th>5 Days</th>
<th>10 Days</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAXLOVID</td>
<td>Placebo</td>
<td>PAXLOVID</td>
<td>Placebo</td>
<td>PAXLOVID</td>
<td>Placebo</td>
<td>PAXLOVID</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=1038</td>
<td>n (%)</td>
<td>N=1053</td>
<td>n (%)</td>
<td>N=540</td>
<td>n (%)</td>
<td>N=528</td>
<td>n (%)</td>
<td>N=912</td>
<td>N=911</td>
<td>N=898</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>48 (4.6)</td>
<td>1 (0.1)</td>
<td>30 (5.6)</td>
<td>2 (0.4)</td>
<td>54 (5.9)</td>
<td>62 (6.8)</td>
<td>6 (0.7)</td>
<td>6 (0.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31 (3.0)</td>
<td>16 (1.5)</td>
<td>22 (4.1)</td>
<td>16 (3.0)</td>
<td>23 (2.5)</td>
<td>22 (2.4)</td>
<td>15 (1.7)</td>
<td>15 (1.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin D dimer increased</td>
<td>22 (2.1)</td>
<td>30 (2.8)</td>
<td>6 (1.1)</td>
<td>6 (1.1)</td>
<td>18 (2.0)</td>
<td>13 (1.4)</td>
<td>4 (0.4)</td>
<td>4 (0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>17 (1.6)</td>
<td>27 (2.6)</td>
<td>13 (2.4)</td>
<td>8 (1.5)</td>
<td>23 (4.1)</td>
<td>21 (2.4)</td>
<td>11 (1.2)</td>
<td>11 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (1.4)</td>
<td>19 (1.8)</td>
<td>17 (3.1)</td>
<td>16 (3.0)</td>
<td>16 (1.8)</td>
<td>12 (1.3)</td>
<td>14 (1.6)</td>
<td>14 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine renal clearance decreased</td>
<td>14 (1.3)</td>
<td>16 (1.5)</td>
<td>5 (0.9)</td>
<td>4 (0.8)</td>
<td>9 (1.0)</td>
<td>5 (0.5)</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (1.2)</td>
<td>13 (1.2)</td>
<td>6 (1.1)</td>
<td>6 (1.1)</td>
<td>15 (1.6)</td>
<td>17 (1.9)</td>
<td>29 (3.2)</td>
<td>29 (3.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (1.2)</td>
<td>9 (0.9)</td>
<td>10 (1.9)</td>
<td>11 (2.1)</td>
<td>7 (0.8)</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>10 (1.0)</td>
<td>14 (1.3)</td>
<td>7 (1.3)</td>
<td>4 (0.8)</td>
<td>2 (0.2)</td>
<td>5 (0.5)</td>
<td>7 (0.8)</td>
<td>7 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Most Frequent (≥1% in EPIC-HR) All-Causality AEs*
Safety Surveillance Under EUA

- The following adverse reactions have been identified by the Office of Surveillance and Epidemiology or the Applicant during use of PAXLOVID under EUA:
  - Immune System Disorders: Anaphylaxis and other hypersensitivity reactions
  - Nervous System Disorders: Headache
  - Vascular Disorders: Hypertension
  - Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
  - General Disorders and Administration Site Conditions: Malaise
PAXLOVID Safety Conclusions

• PAXLOVID demonstrated an overall favorable safety profile in the EPIC-HR, EPIC-SR, and EPIC-PEP clinical trials
  – Note that concomitant use of medications with clinically significant PAXLOVID drug-drug interactions was prohibited in EPIC-HR, EPIC-SR, and EPIC-PEP; therefore, drug interaction risk cannot be assessed through the Phase 3 clinical trial data
Key Issues

Efficacy Issues

• Efficacy of PAXLOVID in high-risk adults who are vaccinated against COVID-19 or had a prior SARS-CoV-2 infection
  Stephanie Troy, MD

• Efficacy of PAXLOVID in the setting of the SARS-CoV-2 Omicron variant
  Jonathan Rawson, PhD

• Impact of PAXLOVID on COVID-19 rebound
  Patrick Harrington, PhD

• Optimal duration of PAXLOVID treatment in immunocompromised patients
  Stephanie Troy, MD

Safety Issue

• Serious adverse reactions due to drug-drug interactions (DDIs)
  Stephanie Troy, MD
Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Had a Prior SARS-CoV-2 Infection

Stephanie Troy, MD, Clinical Reviewer
Jie Cong, PhD, Statistical Reviewer
Patrick Harrington, PhD, Clinical Virology Reviewer
Natasha Pratt, PhD, Epidemiology Reviewer
Jiwei He, PhD, Statistical Reviewer
Thamban Valappil, PhD, Supervisory Mathematical Statistician
Jules O’Rear, PhD, Clinical Virology Team Leader
Yong Ma, PhD, Lead Mathematical Statistician
Sarah Connelly, MD, Cross-Discipline Team Leader
Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Had a Prior SARS-CoV-2 Infection

EPIC-HR Enrollment Period: July 16 to November 6, 2021

Figures adapted from CDC graphs showing cumulative COVID-19 administered vaccine doses (left) and cumulative COVID-19 cases (right) in the U.S. over time from https://covid.cdc.gov/covid-data-tracker/#vaccination-trends and https://covid.cdc.gov/covid-data-tracker/#trends_totalcases_select_00 (accessed February 17, 2023)
Pivotal Efficacy Data Supporting NDA

EPIC-HR Efficacy Results (mITT1\(^a\))

<table>
<thead>
<tr>
<th>Primary endpoint(^\text{b}): COVID-19 related hospitalization or death from any cause through Day 28, n (%)</th>
<th>PAXLOVID (N=977)</th>
<th>PLACEBO (N=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (0.9%)</td>
<td>64 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>COVID-19 related hospitalization through Day 28, n (%)</td>
<td>9 (0.9%)</td>
<td>63 (6.4%)</td>
</tr>
<tr>
<td>All-cause mortality through Day 28, n (%)</td>
<td>0</td>
<td>12 (1.2%)</td>
</tr>
</tbody>
</table>

\(^a\) Subjects dosed within 5 days of symptom onset who did not receive nor were expected to receive therapeutic mAb treatment
\(^\text{b}\) Determination of efficacy was based on interim analysis in mITT population (p-value<0.0001) using Kaplan-Meier estimates (subjects with no events were censored at the time of study discontinuation)

• With PAXLOVID versus placebo, for the primary endpoint:
  – Relative risk reduction (RRR): **86%** (95% CI: 72%, 93%)
  – Absolute risk reduction (ARR): **5.6%** (95% CI: 4.0%, 7.3%)
• Population: **unvaccinated adults with no prior confirmed SARS-CoV-2 infections**
Baseline SARS-CoV-2 Immunity* in U.S. by 2023

• U.S. COVID-19 Vaccination Status as of February 16, 2023¹
  – Completed primary series²: 79% all adults, 94% adults ≥65-years-old
  – Received bivalent booster: 19% all adults, 41% adults ≥65-years-old

• Estimates of Prior SARS-CoV-2 Infection
  – In EPIC-PEP (household contact study that enrolled from September 9, 2021 to March 1, 2022), 12% of subjects had received ≥1 COVID-19 vaccine dose, but 91% were seropositive at baseline
  – Even unvaccinated individuals were likely to be seropositive by 2022 (presumably from prior infection)

*Baseline SARS-CoV-2 immunity here refers to prior receipt of COVID-19 vaccination or SARS-CoV-2 seropositivity (i.e., detectable serum antibodies against SARS-CoV-2).

1. Information taken from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-count-pop12 on February 16, 2023
2. 92% all adults and 95% adults ≥65-years-old in the U.S. have received ≥1 vaccine dose
Benefit in Subjects With Baseline SARS-CoV-2 Immunity: Clinical Trial Data

Data Analyzed in Following Subgroups:

- **Vaccinated high-risk subgroup in EPIC-SR (n=631)**
  - Not powered for the hospitalization/death endpoint, and enrollment of this group ended after PAXLOVID was available through EUA

- **SARS-CoV-2 seropositive subgroup in EPIC-HR (n=969)**
  - May represent pre-existing immunity due to prior infection

- **SARS-CoV-2 seronegative subgroup in EPIC-HR (n=972)**
  - Reference group for comparison
COVID-19-Related Hospitalization or Death From Any Cause Through Day 28
COVID-19-Related Hospitalization or Death From Any Cause Through Day 28

- EPIC-SR mITT1 vaccinated high-risk subgroup: <1% for PAXLOVID, 2% for Placebo
- EPIC-HR mITT1 seropositive subgroup: <1% for PAXLOVID, 2% for Placebo
- EPIC-HR mITT1 seronegative subgroup: 2% for PAXLOVID, 11% for Placebo

Relative Risk Reduction (RRR): 58%, 88%, 85%
COVID-19-Related Hospitalization or Death From Any Cause Through Day 28

Proportion of Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion</th>
<th>RRR</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC-SR mITT1 vaccinated high-risk subgroup</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1.3% (7/314 vs 3/317, p*=0.2)</td>
</tr>
<tr>
<td>EPIC-HR mITT1 seropositive subgroup</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1.5% (8/479 vs 1/490, p*=0.02)</td>
</tr>
<tr>
<td>EPIC-HR mITT1 seronegative subgroup</td>
<td>2%</td>
<td>11%</td>
<td>10% (56/497 vs 8/475, p*&lt;0.0001)</td>
</tr>
</tbody>
</table>

*All displayed p-values are nominal (not adjusted for multiplicity, based on difference in estimated proportions using the Kaplan-Meier Method)
SARS-CoV-2 RNA Levels Over Time

PAXLOVID led to significantly greater reductions in nasopharyngeal (NP) SARS-CoV-2 RNA levels versus placebo from baseline to Day 5 in all 3 subgroups.

Abbreviations: LLOQ, lower limit of quantification
Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Had a Prior SARS-CoV-2 Infection: Conclusion

- 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.

- Pre-existing SARS-CoV-2 immunity is among the many factors that impact the risk of progression to severe COVID-19.
Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

Jonathan Rawson, PhD, Clinical Virology Reviewer
Patrick Harrington, PhD, Clinical Virology Reviewer
Stephanie Troy, MD, Clinical Reviewer
Jiwei He, PhD, Statistical Reviewer
Jules O’Rear, PhD, Clinical Virology Team Leader
Natasha Pratt, PhD, Epidemiology Reviewer
Yong Ma, PhD, Lead Mathematical Statistician
Sarah Connelly, MD, Cross-Discipline Team Leader
Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant

• In EPIC-HR (2021), 99% of subjects were infected with the SARS-CoV-2 Delta variant, but nearly all infections in the United States today are caused by the Omicron variant.

• In the first half of EPIC-SR (2021), 98% of subjects were infected with the SARS-CoV-2 Delta variant. In the second half of EPIC-SR (2022), 100% of subjects were infected with the SARS-CoV-2 Omicron variant (mostly BA.2 and BA.2.12.1), but high-risk subjects could not be enrolled during this time period.

• To determine whether PAXLOVID is likely to retain efficacy in the setting of the SARS-CoV-2 Omicron variant, we evaluated nonclinical virology, genomic surveillance, and clinical virology data, as well as real-world evidence studies conducted during the Omicron time period.
Nirmatrelvir Activity Against SARS-CoV-2 M\textsuperscript{pro} Protease With Natural Amino Acid Polymorphisms

<table>
<thead>
<tr>
<th>M\textsuperscript{pro} Polymorphism*</th>
<th>Cumulative Frequency (as of 11/30/2022)</th>
<th>Geomean K\textsubscript{i} Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>P132H</td>
<td>45.5%</td>
<td>0.7</td>
</tr>
<tr>
<td>K90R</td>
<td>1.4%</td>
<td>1.2</td>
</tr>
<tr>
<td>L89F</td>
<td>1.2%</td>
<td>2.1</td>
</tr>
<tr>
<td>T169S</td>
<td>0.5%</td>
<td>1.1</td>
</tr>
<tr>
<td>P108S</td>
<td>0.2%</td>
<td>2.9</td>
</tr>
<tr>
<td>A260V</td>
<td>0.2%</td>
<td>0.6</td>
</tr>
<tr>
<td>G15S</td>
<td>0.2%</td>
<td>1.6</td>
</tr>
<tr>
<td>L75F</td>
<td>0.2%</td>
<td>0.3</td>
</tr>
<tr>
<td>K88R</td>
<td>0.2%</td>
<td>0.5</td>
</tr>
<tr>
<td>T21I</td>
<td>0.1%</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*L30I and T45N are not listed because they had cumulative frequencies <0.1%.

- In biochemical assays, nirmatrelvir retained activity (K\textsubscript{i} fold-change <3) against recombinant SARS-CoV-2 M\textsuperscript{pro} protease containing the most frequent natural amino acid polymorphisms, including P132H (consensus in Omicron variants)
Nirmatrelvir Activity Against Different SARS-CoV-2 Variants in Cell Culture

<table>
<thead>
<tr>
<th>SARS-CoV-2 Variant</th>
<th>M\textsuperscript{Pro} Polymorphism(s)</th>
<th>Geomean EC\textsubscript{50} (nM)</th>
<th>EC\textsubscript{50} Value Fold-Change</th>
<th>Geomean EC\textsubscript{90} (nM)</th>
<th>EC\textsubscript{90} Value Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA-WA1/2020</td>
<td>N/A</td>
<td>70</td>
<td>N/A</td>
<td>211</td>
<td>N/A</td>
</tr>
<tr>
<td>Omicron BA.2</td>
<td>P132H</td>
<td>65</td>
<td>0.9</td>
<td>132</td>
<td>0.6</td>
</tr>
<tr>
<td>Omicron BA.2.12.1</td>
<td>P132H</td>
<td>40</td>
<td>0.6</td>
<td>114</td>
<td>0.5</td>
</tr>
<tr>
<td>Omicron BA.4</td>
<td>P132H</td>
<td>39</td>
<td>0.6</td>
<td>98</td>
<td>0.5</td>
</tr>
<tr>
<td>Omicron BA.5</td>
<td>P132H</td>
<td>44</td>
<td>0.6</td>
<td>178</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Source: Applicant report. Data are from Vero E6-TMPRSS2 cells treated with a P-glycoprotein inhibitor. Abbreviations: EC\textsubscript{50}, half maximal effective concentration; N/A, not applicable.

- In cell culture, nirmatrelvir retained activity (EC\textsubscript{50} value fold-change <3) against different SARS-CoV-2 variants, including Alpha, Gamma, Delta, Lambda, Mu, and Omicron BA.1, BA.2, BA.2.12.1, BA.4, and BA.5.

- Independent groups have also reported that nirmatrelvir retains activity against different SARS-CoV-2 variants in cell culture, including Omicron BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.5, BQ.1.1, and XBB.
Conservation of SARS-CoV-2 M\textsuperscript{pro} Protease and Cleavage Sites

• Bioinformatic analyses of SARS-CoV-2 M\textsuperscript{pro} protease and cleavage sites were provided based on the GISAID EpiCoV database (n=12.7 million sequences through November 30, 2022)

• Only 10 M\textsuperscript{pro} protease polymorphisms had a cumulative frequency ≥0.1% (range: 0.1-1.4%, excluding P132H); nirmatrelvir retained activity against M\textsuperscript{pro} enzymes with these polymorphisms in biochemical assays (K\textsubscript{i} fold-change <3)

• Only 5 M\textsuperscript{pro} cleavage site (P5-P5' positions) polymorphisms had a cumulative frequency ≥0.1% (range: 0.1-0.5%); M\textsuperscript{pro} cleavage site substitutions have not been associated with nirmatrelvir resistance in cell culture (except for two near the M\textsuperscript{pro} protease C-terminus, which overlaps a cleavage site)

• Overall, these analyses demonstrate that SARS-CoV-2 M\textsuperscript{pro} protease and cleavage site sequences are highly conserved and that nirmatrelvir is expected to retain activity against Omicron variants
Effect of PAXLOVID on SARS-CoV-2 RNA Shedding

In EPIC-SR, PAXLOVID led to significantly greater reductions in SARS-CoV-2 RNA shedding in nasopharyngeal swab samples in both the 2021/pre-Omicron and 2022/Omicron periods, in terms of both average RNA levels and the proportions of samples <LLOQ on Day 5.

Data represent means and 95% confidence intervals.
Abbreviations: BL, baseline; cp/mL, copies per milliliter; EOT, end-of-treatment; LLOQ, lower limit of quantification

- In EPIC-SR, PAXLOVID led to significantly greater reductions in SARS-CoV-2 RNA shedding in nasopharyngeal swab samples in both the 2021/pre-Omicron and 2022/Omicron periods, in terms of both average RNA levels and the proportions of samples <LLOQ on Day 5.
Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant: Conclusion

• Based on nonclinical virology, genomic surveillance, and clinical virology data, PAXLOVID is expected to retain activity against currently circulating SARS-CoV-2 Omicron subvariants

• Real-world evidence reports in the literature have concluded that PAXLOVID retains effectiveness (in terms of preventing hospitalization and death) against the SARS-CoV-2 Omicron variant; however, these reports did not include sufficient information to allow for a complete review
Impact of PAXLOVID on COVID-19 Rebound

Patrick Harrington, PhD, Clinical Virology Reviewer
Jie Cong, PhD, Statistical Reviewer
Stephanie Troy, MD, Clinical Reviewer
Yan Li, PhD, Epidemiology Reviewer
Jules O’Rear, PhD, Clinical Virology Team Leader
Thamban Valappil, PhD, Supervisory Mathematical Statistician
Natasha Pratt, PhD, Epidemiology Team Leader
Sarah Connelly, MD, Cross-Discipline Team Leader
FDA Assessment of COVID-19 Rebound

• FDA is in alignment with the Applicant on the impact of PAXLOVID on COVID-19 rebound
  – Analyses of the EPIC-HR and EPIC-SR trials showed a subset of PAXLOVID- and Placebo-treated subjects experienced virologic and/or symptomatic rebound after end-of-treatment/Day 5.
  – No clear or consistent association between virologic or symptomatic rebound and PAXLOVID use.

• Independent FDA analyses of COVID-19 rebound in EPIC-HR and EPIC-SR:
  – Viral RNA rebound
  – Symptom rebound
  – Combined viral RNA + symptom rebound
Post-Treatment Nasopharyngeal (NP) Viral RNA Rebound: Definitions

- **Day 10 Rebound**: Day 5 <LLOQ AND at Day 10 ≥LLOQ, OR, Day 5 ≥LLOQ AND Day 10 ≥0.5 log_{10} copies/mL increase from Day 5
- **Day 14 Rebound**: Day 5 <LLOQ AND at Day 14 ≥LLOQ, OR, Day 5 ≥LLOQ AND Day 14 ≥0.5 log_{10} copies/mL increase from Day 5
- **Day 10 or Day 14 Rebound**: Viral RNA rebound from Day 5 to either Day 10 OR Day 14

Analysis Notes:
- Analysis definitions intended to detect occurrences of post-treatment increases in viral RNA, regardless of magnitude. The clinical relevance of any specific level of viral RNA rebound has not been established.
- EPIC-HR mITT2 and EPIC-SR mITT1 populations (all treated subjects)
- RNA <LLOQ (<2 log_{10} copies/mL) imputed to 1.7 log_{10} copies/mL, Target Not Detected imputed to 0 log_{10} copies/mL
- All denominators based on the numbers of subjects with data at the analysis visit timepoint(s)
- LLOQ, lower limit of quantification
Post-Treatment Nasopharyngeal (NP) Viral RNA Rebound: Definitions

• **Day 10 Rebound:** Day 5 < LLOQ AND at Day 10 ≥ LLOQ, OR, Day 5 ≥ LLOQ AND Day 10 ≥ 0.5 log\(_{10}\) copies/mL increase from Day 5

• **Day 14 Rebound:** Day 5 < LLOQ AND at Day 14 ≥ LLOQ, OR, Day 5 ≥ LLOQ AND Day 14 ≥ 0.5 log\(_{10}\) copies/mL increase from Day 5

• **Day 10 or Day 14 Rebound:** Viral RNA rebound from Day 5 to either Day 10 OR Day 14

Analysis Notes:
• Analysis definitions intended to detect occurrences of post-treatment increases in viral RNA, regardless of magnitude. The clinical relevance of any specific level of viral RNA rebound has not been established.
• EPIC-HR mITT2 and EPIC-SR mITT1 populations (all treated subjects)
• RNA < LLOQ (<2 log\(_{10}\) copies/mL) imputed to 1.7 log\(_{10}\) copies/mL, Target Not Detected imputed to 0 log\(_{10}\) copies/mL
• All denominators based on the numbers of subjects with data at the analysis visit timepoint(s)
• LLOQ, lower limit of quantification
Post-Treatment Nasopharyngeal (NP) Viral RNA Rebound: Definitions

- **Day 10 Rebound**: Day 5 <LLOQ AND at Day 10 ≥LLOQ, OR, Day 5 ≥LLOQ AND Day 10 ≥0.5 log_{10} copies/mL increase from Day 5
- **Day 14 Rebound**: Day 5 <LLOQ AND at Day 14 ≥LLOQ, OR, Day 5 ≥LLOQ AND Day 14 ≥0.5 log_{10} copies/mL increase from Day 5
- **Day 10 or Day 14 Rebound**: Viral RNA rebound from Day 5 to either Day 10 OR Day 14

Analysis Notes:
- Analysis definitions intended to detect occurrences of post-treatment increases in viral RNA, regardless of magnitude. The clinical relevance of any specific level of viral RNA rebound has not been established.
- EPIC-HR mITT2 and EPIC-SR mITT1 populations (all treated subjects)
- RNA <LLOQ (<2 log_{10} copies/mL) imputed to 1.7 log_{10} copies/mL, Target Not Detected imputed to 0 log_{10} copies/mL
- All denominators based on the numbers of subjects with data at the analysis visit timepoint(s)
- LLOQ, lower limit of quantification
Post-Treatment Nasopharyngeal (NP) Viral RNA Rebound: Definitions

- **Day 10 Rebound:** Day 5 < LLOQ AND at Day 10 ≥ LLOQ, OR, Day 5 ≥ LLOQ AND Day 10 ≥ 0.5 \( \log_{10} \) copies/mL increase from Day 5
- **Day 14 Rebound:** Day 5 < LLOQ AND at Day 14 ≥ LLOQ, OR, Day 5 ≥ LLOQ AND Day 14 ≥ 0.5 \( \log_{10} \) copies/mL increase from Day 5
- **Day 10 or Day 14 Rebound:** Viral RNA rebound from Day 5 to either Day 10 OR Day 14

Analysis Notes:
- Analysis definitions intended to detect occurrences of post-treatment increases in viral RNA, regardless of magnitude. The clinical relevance of any specific level of viral RNA rebound has not been established.
- EPIC-HR mITT2 and EPIC-SR mITT1 populations (all treated subjects)
- RNA < LLOQ (<2 \( \log_{10} \) copies/mL) imputed to 1.7 \( \log_{10} \) copies/mL, Target Not Detected imputed to 0 \( \log_{10} \) copies/mL
- All denominators based on the numbers of subjects with data at the analysis visit timepoint(s)
- LLOQ, lower limit of quantification
Viral RNA Rebound in EPIC-HR

PAXLOVID: 6.6% (57/865)  Placebo: 4.7% (40/856)  \( p=0.09^* \)

PAXLOVID: 2.6% (23/884)  Placebo: 1.9% (17/893)  \( p=0.34^* \)

*Nominal p-value (not adjusted for multiplicity), Fisher’s exact test, two-sided
Viral RNA Rebound in EPIC-HR

Day 10 or Day 14 Rebound

PAXLOVID: 8.3% (77/925)  [p=0.04*]
Placebo: 5.7% (53/922)

*Nominal p-value (not adjusted for multiplicity), Fisher’s exact test, two-sided
Viral RNA Rebound in EPIC-HR: Caution in Interpretation of Viral RNA Rebound Rates

• “Rebound” implies first a decrease, followed by an increase in viral RNA.
  – Subjects with Day 10/14 Viral RNA Rebound: 94% (119/126) w/Day 5 RNA <LLOQ, OR ≥1 log_{10} copies/mL decline from Baseline to Day 5

• Subjects treated with PAXLOVID had a greater viral RNA response through Day 5 compared to Placebo-treated subjects.

• Rate of viral RNA rebound could be biased by greater impact of PAXLOVID on early viral RNA decline.
  – To account for this potential bias, viral RNA rebound rates for PAXLOVID and Placebo-treated subjects were assessed for those with comparable virologic responses though Day 5/end-of-treatment (EOT).
Viral RNA Rebound in EPIC-HR

Day 10 or Day 14 Rebound: Day 5 Virologic Responders (Day 5 RNA <LLOQ, OR ≥1 log₁₀ copies/mL decline from BL to Day 5)

PAXLOVID: 8.1% (69/849)
Placebo: 6.5% (50/772)  \[ p=0.22^* \]

*Nominal p-value (not adjusted for multiplicity), Fisher’s exact test, two-sided
Viral RNA Rebound in EPIC-HR:
Not Associated With Hospitalization or Death

Day 10 or 14 Rebound:
4 Subjects w/Hospitalization or Death (n=1 PAXLOVID, n=3 Placebo; no deaths)
Viral RNA Rebound in EPIC-HR: Additional Analyses

• Post-treatment viral RNA rebound was not associated with immunosuppression risk:
  – n=6 PAXLOVID, n=7 Placebo; 1 rebound (Placebo), no hospitalizations or deaths

• Post-treatment viral RNA rebound was generally not associated with resistance:
  – Two (3%) PAXLOVID-treated subjects with Day 10 viral RNA rebound and treatment-emergent M\textsuperscript{pro} E166V or T304I substitutions detected at ~24% variant frequency on Day 10, and viral RNA <LLOQ by Day 14

• Post-treatment viral RNA rebound was associated with detection of cell culture infectious SARS-CoV-2* in a subset of subjects (Applicant’s analyses):
  – Cell culture infectious virus assays: viral recovery and viral titration (50% tissue culture infectious dose [TCID\textsubscript{50}])
  – Among subjects with post-treatment viral RNA rebound (Applicant-defined), similar rate of Day 10 or Day 14 samples from PAXLOVID- and Placebo-treated subjects tested positive for SARS-CoV-2 virus by cell culture:
    ▪ Positive by virus recovery assay: 11% PAXLOVID, 5% Placebo
    ▪ Positive by virus titration (TCID\textsubscript{50}) assay: 23% PAXLOVID, 37% Placebo
    ▪ Positive by either assay: 29%, PAXLOVID, 39% Placebo

*Relationship between viral cell culture infectivity and transmissibility is unclear, but results could indicate transmissible virus is present.
Viral RNA Rebound Rates (Day 10 or Day 14) Across EPIC-HR and EPIC-SR

*Nominal p-values (not adjusted for multiplicity), Fisher's exact test, two-sided

EPIC-HR and EPIC-SR (2021/Pre-Omicron): SARS-CoV-2 Delta variants detected in 98-99% of subjects with available data.

EPIC-SR (2022/Omicron): SARS-CoV-2 Omicron variants detected in 100% of subjects with available variant data (195/195, including 7 with Omicron-containing recombinants)
**SARS-CoV-2 RNA ≥LLOQ at Each Visit**

At all analysis timepoints, relative to Placebo recipients, PAXLOVID recipients were less likely to have viral RNA ≥LLOQ, regardless of any differences in rebound rates from Day 5 to Days 10/14.

<table>
<thead>
<tr>
<th></th>
<th>Day 3</th>
<th>Day 5/EOT</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPIC-HR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAXLOVID</td>
<td>64.9%</td>
<td>52.2%</td>
<td>31.1%</td>
<td>52.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>67.2%</td>
<td>55.9%</td>
<td>34.0%</td>
<td>35.9%</td>
</tr>
<tr>
<td><strong>EPIC-SR (2021/Pre-Omicron)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAXLOVID</td>
<td>68.5%</td>
<td>59.6%</td>
<td>22.7%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Placebo</td>
<td>69.7%</td>
<td>50.7%</td>
<td>27.9%</td>
<td>40.0%</td>
</tr>
<tr>
<td><strong>EPIC-SR (2022/Omicron)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAXLOVID</td>
<td>67.6%</td>
<td>43.4%</td>
<td>13.6%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>81.0%</td>
<td>43.4%</td>
<td>13.6%</td>
<td>22.5%</td>
</tr>
</tbody>
</table>
Viral RNA “Rebound” On-Treatment

Higher frequency of viral RNA “rebound” on-treatment indicates elevations in viral RNA could reflect natural or technical variability, not necessarily virologic “relapse” after stopping treatment.
Symptom ± Viral RNA Rebound: Analysis Definitions

Symptom rebound definitions
• **Short symptom recovery**: First day of \( \geq 2 \) consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
• **Symptom rebound**: *After* short symptom recovery, \( \geq 2 \) consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
• **Moderate symptom rebound**: Among those with symptom rebound, having (a) \( \geq 1 \) moderate or severe rebound symptom (b) \( \geq 2 \) symptoms during a day of rebound, or (c) hospitalization/death

Symptomatic viral RNA rebound definitions
• **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or \( \geq 1 \) log\(_{10}\) copy/mL decline from baseline), AND short symptom recovery by Day 14.
• **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

Limitations of analyses
• Extensive fluctuation in self-reported symptoms
• Data quality issues (e.g., high frequency of missing symptom data)
• Viral RNA data not captured daily to link with daily symptom reporting
• Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

Symptom rebound definitions
• **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
• **Symptom rebound**: After short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
• **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

Symptomatic viral RNA rebound definitions
• **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log_{10} copy/mL decline from baseline), AND short symptom recovery by Day 14.
• **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

Limitations of analyses
• Extensive fluctuation in self-reported symptoms
• Data quality issues (e.g., high frequency of missing symptom data)
• Viral RNA data not captured daily to link with daily symptom reporting
• Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

**Symptom rebound definitions**

- **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
- **Symptom rebound**: *After* short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
- **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

**Symptomatic viral RNA rebound definitions**

- **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log₁₀ copy/mL decline from baseline), AND short symptom recovery by Day 14.
- **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

**Limitations of analyses**

- Extensive fluctuation in self-reported symptoms
- Data quality issues (e.g., high frequency of missing symptom data)
- Viral RNA data not captured daily to link with daily symptom reporting
- Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

**Symptom rebound definitions**
- **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
- **Symptom rebound**: After short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
- **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

**Symptomatic viral RNA rebound definitions**
- **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log_{10} copy/mL decline from baseline), AND short symptom recovery by Day 14.
- **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

**Limitations of analyses**
- Extensive fluctuation in self-reported symptoms
- Data quality issues (e.g., high frequency of missing symptom data)
- Viral RNA data not captured daily to link with daily symptom reporting
- Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

Symptom rebound definitions
• **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
• **Symptom rebound**: After short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
• **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

Symptomatic viral RNA rebound definitions
• **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log_{10} copy/mL decline from baseline), AND short symptom recovery by Day 14.
• **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

Limitations of analyses
• Extensive fluctuation in self-reported symptoms
• Data quality issues (e.g., high frequency of missing symptom data)
• Viral RNA data not captured daily to link with daily symptom reporting
• Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

Symptom rebound definitions
• **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
• **Symptom rebound**: After short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
• **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

Symptomatic viral RNA rebound definitions
• **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log_{10} copy/mL decline from baseline), AND short symptom recovery by Day 14.
• **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

Limitations of analyses
• Extensive fluctuation in self-reported symptoms
• Data quality issues (e.g., high frequency of missing symptom data)
• Viral RNA data not captured daily to link with daily symptom reporting
• Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom ± Viral RNA Rebound: Analysis Definitions

Symptom rebound definitions
- **Short symptom recovery**: First day of ≥2 consecutive diary entries where all targeted symptoms were absent (and not hospitalized prior to symptom recovery)
- **Symptom rebound**: After short symptom recovery, ≥2 consecutive diary entries (after Day 5/EOT) with any targeted symptom regardless of severity, or hospitalization, through Day 28
- **Moderate symptom rebound**: Among those with symptom rebound, having (a) ≥1 moderate or severe rebound symptom (b) ≥2 symptoms during a day of rebound, or (c) hospitalization/death

Symptomatic viral RNA rebound definitions
- **Combined recovery**: Virologic responder on Day 5 (<LLOQ at Day 5 or ≥1 log_{10} copy/mL decline from baseline), AND short symptom recovery by Day 14.
- **Symptomatic viral RNA rebound**: Among those with combined recovery, viral RNA rebound through Day 14, AND symptom rebound at any time after symptom recovery.

Limitations of analyses
- Extensive fluctuation in self-reported symptoms
- Data quality issues (e.g., high frequency of missing symptom data)
- Viral RNA data not captured daily to link with daily symptom reporting
- Majority of symptom rebounds occurred after Day 14, while viral RNA data were only available through Day 14
Symptom Rebound Through Day 28

<table>
<thead>
<tr>
<th></th>
<th>% of Subjects with Symptom Rebound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Rebound (Any)</strong></td>
<td>PAXLOVID</td>
</tr>
<tr>
<td>90/768</td>
<td>11.7%</td>
</tr>
<tr>
<td>54/768</td>
<td>7.0%</td>
</tr>
<tr>
<td>59/706</td>
<td>15.8%</td>
</tr>
<tr>
<td>65/411</td>
<td>9.7%</td>
</tr>
<tr>
<td>40/111</td>
<td>10.4%</td>
</tr>
<tr>
<td>12/88</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

| **Moderate Symptom Rebound** | PAXLOVID | Placebo     |
| 98/706                    | 13.9%    | 10.2%       |
| 59/706                    | 8.4%     | 4.2%        |
| 57/404                    | 14.1%    | 13.6%       |
| 41/404                    | 10.1%    | 10.2%       |
| 12/88                     | 4.2%     | 10.2%       |

**EPIC-HR**

**EPIC-SR (2021/Pre-Omicron)**

**EPIC-SR (2022/Omicron)**
## Combined Symptom + Viral RNA Rebound

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAXLOVID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC-HR, N</td>
<td>1029</td>
<td>1045</td>
</tr>
<tr>
<td>Combined recovery, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>470 (45.7)</td>
<td>385 (36.8)</td>
</tr>
<tr>
<td><strong>Symptomatic viral RNA rebound, n (%)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>4 (0.9)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>EPIC-SR 2021 (Pre-Omicron), N</td>
<td>533</td>
<td>527</td>
</tr>
<tr>
<td>Combined recovery, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>292 (54.8)</td>
<td>232 (44.0)</td>
</tr>
<tr>
<td><strong>Symptomatic viral RNA rebound, n (%)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>3 (1.0)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>EPIC-SR 2022 (Omicron), N</td>
<td>114</td>
<td>106</td>
</tr>
<tr>
<td>Combined recovery, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62 (54.4)</td>
<td>55 (51.9)</td>
</tr>
<tr>
<td><strong>Symptomatic viral RNA rebound, n (%)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Percentage over total subjects.

<sup>b</sup> Percentage over those who achieved combined recovery.
Impact of PAXLOVID on COVID-19 Rebound: Conclusion

Based on analyses of virology and clinical outcome data from clinical trials EPIC-HR and EPIC-SR, rebound in SARS-CoV-2 (RNA or virus) shedding or COVID-19 symptoms occurs in a subset of infections, is not clearly associated with PAXLOVID treatment, is not associated with severe disease outcomes, and likely reflects natural COVID-19 disease progression and/or technical variability in virology assessments.
Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

Stephanie Troy, MD, Clinical Reviewer
Ye Xiong, PhD, Pharmacometrics Reviewer
Cristina Miglis, PharmD, MS, Clinical Pharmacology Reviewer
Patrick Harrington, PhD, Clinical Virology Reviewer
Jiang Liu, PhD, Pharmacometrics Team Leader
Yuching Yang, PhD, Pharmacometrics Team Leader
Mario Sampson, PharmD, Clinical Pharmacology Team Leader
Jules O’Rear, PhD, Clinical Virology Team Leader
Sarah Connelly, MD, Cross-Discipline Team Leader
The highly immunocompromised population can have unique COVID-19 manifestations such as persistent SARS-CoV-2 infection:

- Persistent SARS-CoV-2 infection for ≥30 days was reported in 14% of patients with hematologic malignancies at one center\(^1\) (versus most patients clearing infection by 10 days in the general population)

- Persistent infection can lead to morbidity and mortality from COVID-19 as well as interruption to clinical care for other conditions (chemotherapy, delay in transplant, etc.)

PAXLOVID in Immunocompromised Patients: Available Clinical Data

- EPIC-HR: <1% of subjects (n=13) were classified as having immunosuppression
  - None met the primary endpoint (hospitalization/death)
  - None of the six randomized to PAXLOVID had evidence of increased SARS-CoV-2 RNA levels after treatment was stopped on Day 5

- >20 severely immunosuppressed patients with persistent SARS-CoV-2 infection (up to 6 months) have received 10 to 28 days of PAXLOVID under emergency INDs. **Of the 15 with outcome data:**
  - **Two died** (one of COVID-19 pneumonia who was in ICU at baseline, one with cavitary pulmonary aspergillosis and decreasing SARS-CoV-2 RNA level at time of death)
  - **Eleven reported clinical improvement or complete resolution of symptoms**, of whom five also reported viral clearance (no information about viral clearance reported for the other six)
    - Two of these patients have been published as case reports
  - **Two reported viral clearance only** (one with persistent symptoms, one with no information on symptoms)

Small numbers, along with concomitant administration of other SARS-CoV-2 antivirals (e.g., remdesivir), wide range of clinical presentations, and lack of a control group limit the interpretation of these results.

Applicant’s QSP Modeling and Simulation

Modeling

• Quantitative Systems Pharmacology (QSP) model leverages existing mechanistic knowledge to mathematically represent the disease pathophysiology of viral replication and immune response.
• Model parameters were partially informed by studies in the literature.
• Virtual patients were calibrated and validated with data from multiple observational studies and three randomized controlled trials of other anti-viral products to represent pathophysiological heterogeneity in population.

Modeling Application – select the duration of treatment in trials

• Simulation for general population, further calibrated by EPIC-HR data
• Simulation for immunocompromised (IC) population: Two virtual IC populations were generated to assess viral RNA suppression with various dosing periods, in comparison with 5-day dosing using:
  • “induced”: 50% effect of Type I IFN and CD8+ T cells
  • “resembling”: top 85th viral shedding duration
“Induced” IC scenario presents a prolonged viral shedding qualitatively similar to the profile of “resembling” IC virtual population.

By 5 days of treatment, the average predicted viral load in IC patients is substantially higher than that in nominal patients (general high-risk population), suggesting the treatment period of 5 days may not be optimal for IC patients.

From viral reduction perspective, 10 days treatment is at plateau for two IC virtual populations based on the defined criteria.

Summary graph of EPIC-IC QSP model
Clinical trial data are needed to determine the optimal PAXLOVID treatment duration in the immunocompromised population, particularly as a longer treatment duration may impact DDI management in this population.

Data from the ongoing clinical trial EPIC-IC will help determine the optimal duration in this population:
- EPIC-IC is a randomized, double-blind clinical trial in which immunocompromised subjects with mild to moderate COVID-19 are randomized to 5, 10, or 15 days of PAXLOVID treatment.
- See [https://clinicaltrials.gov/ct2/show/NCT05438602](https://clinicaltrials.gov/ct2/show/NCT05438602)
Serious Adverse Reactions Due to DDIs

Stephanie Troy, MD, Clinical Reviewer
Cristina Miglis, PharmD, MS, Clinical Pharmacology Reviewer
Natasha Pratt, PhD, Epidemiology Reviewer
John Rhee, PharmD, MS, Drug Use Reviewer
Kate McCartan, MD, Division of Pharmacovigilance Reviewer
Mario Sampson, PharmD, Clinical Pharmacology Team Leader
Sheheryar Muhammad, PharmD, Drug Use Team Leader (Acting)
Rachna Kapoor, PharmD, MBA, Division of Pharmacovigilance Team Leader
Sarah Connelly, MD, Cross-Discipline Team Leader
Table 1, Established and Other Potentially Significant Drug Interactions, from the PAXLOVID EUA Fact Sheet for Healthcare Providers https://www.fda.gov/media/155050/download
PAXLOVID DDIs: Overview

PAXLOVID = co-administered nirmatrelvir + ritonavir
– Nirmatrelvir is a SARS-CoV-2 main protease inhibitor
– Ritonavir is a potent CYP3A inhibitor included to increase nirmatrelvir plasma levels

*The DDIs are mainly associated with ritonavir.*

- DDI List in the EUA Fact Sheet for Healthcare Providers, which is **NOT comprehensive**, includes **143** separate drugs with PAXLOVID DDIs, of which:
  - **37** are contraindicated with PAXLOVID
  - **21** are not contraindicated but have an avoid concomitant use recommendation
  - **49** have a recommendation for a dose adjustment
  - **6** have a recommendation for therapeutic drug concentration or pharmacodynamic laboratory marker monitoring (e.g., warfarin and tacrolimus)
Risk of Serious Adverse Reactions Due to PAXLOVID DDIs: Available Data

• Concomitant use of medications with clinically significant PAXLOVID DDIs was prohibited in EPIC-HR, EPIC-SR, and EPIC-PEP
  – Risk cannot be assessed through the Phase 3 clinical trial data

• Three safety surveillance analyses conducted by Office of Surveillance and Epidemiology (OSE) during the time period since PAXLOVID has been available under EUA:
  1. Proportion of PAXLOVID-eligible population taking drugs with PAXLOVID DDIs
  2. Types of providers prescribing PAXLOVID in the United States
  3. Reports of serious adverse events assessed as probably or possibly related to DDIs included in labeling
Use of Concomitant Medications (DDI Drugs) in PAXLOVID-eligible Patients and PAXLOVID Users

<table>
<thead>
<tr>
<th></th>
<th>COVID-19 patients 65+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment</th>
<th>COVID-19 patients 50+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment</th>
<th>PAXLOVID users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>%</td>
<td>Count</td>
</tr>
<tr>
<td>Medicare (12/22/2021-9/10/2022)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>1,829,342</td>
<td>100.0%</td>
<td>1,844,062</td>
</tr>
<tr>
<td>Any DDI drugs</td>
<td>1,227,485</td>
<td>67.1%</td>
<td>1,234,817</td>
</tr>
<tr>
<td>Other*</td>
<td>781,883</td>
<td>42.7%</td>
<td>787,613</td>
</tr>
<tr>
<td>Avoid Concomitant Use</td>
<td>715,805</td>
<td>39.1%</td>
<td>717,679</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>215,581</td>
<td>11.8%</td>
<td>216,960</td>
</tr>
<tr>
<td>VA (01/01/2022-10/31/2022)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>169,235</td>
<td>100.0%</td>
<td>206,879</td>
</tr>
<tr>
<td>Any DDI drugs</td>
<td>110,370</td>
<td>65.2%</td>
<td>117,242</td>
</tr>
<tr>
<td>Other*</td>
<td>78,800</td>
<td>46.6%</td>
<td>84,000</td>
</tr>
<tr>
<td>Avoid Concomitant Use</td>
<td>68,434</td>
<td>40.4%</td>
<td>71,186</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>15,218</td>
<td>9.0%</td>
<td>15,839</td>
</tr>
</tbody>
</table>

*Other includes DDI drugs with recommended actions like dose modification, laboratory monitoring, and clinical monitoring.
## Top 10 DDI Drug Use in PAXLOVID-Eligible Patients (VA)

<table>
<thead>
<tr>
<th>PAXLOVID DDI drug</th>
<th>Recommended Action for DDI</th>
<th>COVID-19 patients 65+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment</th>
<th>COVID-19 patients 50+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total N</strong></td>
<td></td>
<td>169,235</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Any DDI drugs</strong></td>
<td></td>
<td><strong>110,370</strong></td>
<td>65.2%</td>
</tr>
<tr>
<td>ATORVASTATIN</td>
<td>Avoid Concomitant Use</td>
<td>39321</td>
<td>23.2%</td>
</tr>
<tr>
<td>AMLODIPINE</td>
<td>Other*</td>
<td>24,834</td>
<td>14.7%</td>
</tr>
<tr>
<td>TAMSULOSIN</td>
<td>Avoid Concomitant Use</td>
<td>19512</td>
<td>11.5%</td>
</tr>
<tr>
<td>SILDENAFIL</td>
<td>Other</td>
<td>14,414</td>
<td>8.5%</td>
</tr>
<tr>
<td>FLUTICASONE</td>
<td>Other</td>
<td>13,867</td>
<td>8.2%</td>
</tr>
<tr>
<td>ROSUVASTATIN</td>
<td>Avoid Concomitant Use</td>
<td>10877</td>
<td>6.4%</td>
</tr>
<tr>
<td>TRAZODONE</td>
<td>Other</td>
<td>10,099</td>
<td>6.0%</td>
</tr>
<tr>
<td>SIMVASTATIN</td>
<td>Contraindicated Drug</td>
<td>9,045</td>
<td>5.3%</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>Other</td>
<td>7,806</td>
<td>4.6%</td>
</tr>
<tr>
<td>SALMETEROL</td>
<td>Avoid Concomitant Use</td>
<td>7,376</td>
<td>4.4%</td>
</tr>
<tr>
<td>BUPROPION</td>
<td>Other</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Other includes actions like dose modification, laboratory monitoring, and clinical monitoring.
Drug Utilization Top Specialties

<table>
<thead>
<tr>
<th>Total Paxlovid Prescriptions</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Practice/General Practice/Internal Medicine</td>
<td>6,271,340</td>
<td>74.4%</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>605,452</td>
<td>7.2%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>219,455</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>192,458</td>
<td>2.3%</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>92,538</td>
<td>1.1%</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>405</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>All Other Specialties</td>
<td>543,741</td>
<td>6.5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>501,994</td>
<td>6.0%</td>
</tr>
</tbody>
</table>


Estimated number of PAXLOVID prescriptions dispensed from U.S. outpatient pharmacies*, stratified by top prescriber specialties, week ending on December 31, 2021, through week ending on January 13, 2023, aggregated

*Outpatient pharmacies include retail, long-term care, and mail-order/specialty pharmacies.
Reports of Serious Adverse Events Due to PAXLOVID DDIs That Are Included in Labeling*

- From PAXLOVID authorization (December 22, 2021) through January 30, 2023, OSE analyzed adverse events following PAXLOVID use for the treatment of COVID-19 reported to:
  - FAERS (FDA Adverse Events Reporting System)
  - The FACT (FDA-American College of Medical Toxicology COVID-19 Toxicology Investigators Consortium) Pharmacovigilance Project Sub-registry
  - The medical literature

- **271** cases of serious adverse events assessed as possibly or probably related to PAXLOVID DDIs included in the Fact Sheet for Healthcare Providers, of which:
  - **147** reported hospitalization
  - **6** reported a fatal outcome (4 with tacrolimus, 1 with verapamil, and 1 with both nifedipine and atorvastatin)

***Although reporting requirements are different for a drug under EUA, FAERS is a passive reporting system, so the incidence of adverse events related to PAXLOVID DDIs cannot be calculated based on these data.***

*Labeling here refers to the PAXLOVID EUA Fact Sheet for Healthcare Providers, link: [https://www.fda.gov/media/155050/download](https://www.fda.gov/media/155050/download)*
Reminder: PAXLOVID Benefit in 2023 When Most People in the U.S. Have Some baseline SARS-CoV-2 Immunity

Percentage of Subjects with COVID-19 related hospitalization or death from any cause through Day 28

- **ARR 1.3%** (7/314 vs 3/317, p*=0.2)
- **ARR 1.5%** (8/479 vs 1/490, p*=0.02)
- **ARR 10%** (56/497 vs 8/475, p*<0.0001)

*All displayed p values are nominal (not adjusted for multiplicity, based on difference in estimated proportions using the Kaplan-Meier Method)*
Benefit-Risk Assessment in U.S. in 2023:

- On a **population** level, benefit of PAXLOVID use outweighs risk
  - In January 2023, each week in the U.S. there were still¹:
    - 4000 COVID-19-related deaths
    - 35,000 COVID-19-related hospitalizations
  - Conservative (low) estimate of population benefit: if 75% of high-risk population is not on medications with DDIs that would preclude PAXLOVID treatment, a ~50-90% relative risk reduction could still result in ≥1500 lives saved and ≥13,000 hospitalizations avoided each week with PAXLOVID use.

- However, on an **individual** level, benefit of PAXLOVID will not outweigh risk in all high-risk patients, particularly if the DDIs are not adequately managed.
  - Absolute risk reduction for hospitalization/death in population with some baseline SARS-CoV-2 immunity is ~1-2%.
  - Risk of serious adverse reactions due to DDIs could be >1-2% percent with concomitant use of certain medications.


Top picture taken from Microsoft 365 Stock Images. Bottom picture taken from photo by Amrut Roul on Unsplash.
Benefit-Risk Assessment: One Family

**POSITIVE B/R**

- 79-year-old woman, fully vaccinated & boosted, with arthritis and no DDI.

- 80-year-old man, fully vaccinated & boosted, with hypertension and hyperlipidemia who is on rosuvastatin and amlodipine and is very compliant with medical instructions.

- 52-year-old man, fully vaccinated & boosted, with no significant medical history and no concomitant meds.

**NEGATIVE B/R**

- 81-year-old man, fully vaccinated & boosted, with atrial fibrillation, hypertension, hyperlipidemia, diabetes mellitus, and chronic kidney disease on multiple medications, including amiodarone and rivaroxaban, who is not always compliant with medical instructions.
Serious Adverse Reactions Due to DDIs: Conclusion

• Serious adverse reactions due to DDIs are the key safety concern with PAXLOVID

• Safety surveillance data indicate:
  – >50% PAXLOVID-eligible Medicare and VA patients are on medications with PAXLOVID DDIs (though many of these DDIs could be managed with dose modification, etc.)
  – 74% of PAXLOVID prescriptions were from adult primary care practitioners
  – Serious adverse events due to labeled PAXLOVID DDIs have been reported, including deaths

• To safely prescribe PAXLOVID, all providers MUST*:
  – Review all concomitant medications to assess for PAXLOVID DDIs
  – If PAXLOVID DDIs are identified:
    ✓ Determine if benefit of PAXLOVID outweighs the risks
    ✓ If yes, take appropriate actions to manage the DDIs (e.g., dose adjust or temporarily discontinue the concomitant medication or increase monitoring)

*In addition to other considerations like renal function, hepatic function, and indicated use
Overall Conclusions

• PAXLOVID, an oral drug product, significantly reduced the risk of COVID-19 related hospitalization or all cause death through Day 28 in high-risk adults with mild-to-moderate COVID-19
  – Efficacy seen in adults with baseline SARS-CoV-2 immunity
  – PAXLOVID is expected to retain activity against currently circulating SARS-CoV-2 Omicron subvariants

• No clear association between PAXLOVID use and COVID-19 rebound (may be natural part of COVID-19 clinical course in a small subset of patients)

• More data are needed on optimal PAXLOVID duration in the immunocompromised population (clinical trial, EPIC-IC, ongoing)

• Key safety issue is risk of serious adverse reactions due to PAXLOVID DDIs
Acknowledgements

We would like to thank the many colleagues who contributed greatly to this work both in the Division of Antivirals and Office of Infectious Diseases as well as across CDER review divisions in other offices (including the Office of Clinical Pharmacology, the Office of Biostatistics, the Office of Pharmaceutical Quality, and the Office of Surveillance and Epidemiology and its suboffices).
Charge to the Committee

NDA 217188

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged

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

Antimicrobial Drugs Advisory Committee Meeting
March 16, 2023

Debra Birnkrant, MD
Director, Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research
Proposed indication:

PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death
Background

• COVID-19 is a serious and potentially life-threatening disease
• COVID-19 has evolved since the beginning of the pandemic
• Remdesivir is the only FDA-approved therapy available for the treatment of mild-to-moderate disease
  – Adults and pediatric population at high risk of progression to severe disease
  – 3-day infusion
• PAXLOVID and Molnupiravir are available under emergency use authorization for treatment of mild-to-moderate disease
• PAXLOVID NDA 217188 submitted on June 29, 2022
NDA 217188

• Clinical Trials
  – Three Phase 2/3 trials conducted to support safety and efficacy:
  – EPIC-HR: July 2021- November 2021, VOC Delta
  – EPIC-SR: August 2021- November 2021, VOC Delta
  – March 2022- June 2022, VOC Omicron; data submitted for supporting analyses, including rebound analysis
  – EPIC-PEP: September 2021- March 2022, VOC Delta and Omicron
  – Vaccination limited in trials

• 2023
  – Changing landscape
  – Omicron subvariants predominate
  – Most adults have received vaccine doses or have had infection with SARS-CoV-2
Review Issues

- Efficacy of PAXLOVID in high-risk adults who are vaccinated against COVID-19 or had a prior SARS-CoV-2 infection
- Efficacy of PAXLOVID in the setting of the SARS-CoV-2 Omicron variant
- Impact of PAXLOVID on COVID-19 rebound
- Optimal duration of PAXLOVID treatment in immunocompromised patients
- Serious adverse reactions due to drug-drug interactions
Discussion/Questions

1. Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?
   a. If yes, please provide your rationale.
   b. If no, please provide your rationale and list what additional studies/trials are needed.
Discussion/Questions (2)

2. 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 Omicron subvariants.
   c. Individuals who are immunocompromised.

   Please comment if additional data are needed in these populations.
