U.S. FOOD & DRUG ADMINISTRATION

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.

1- FDA defines mild and moderate COVID-19 consistent with NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

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.

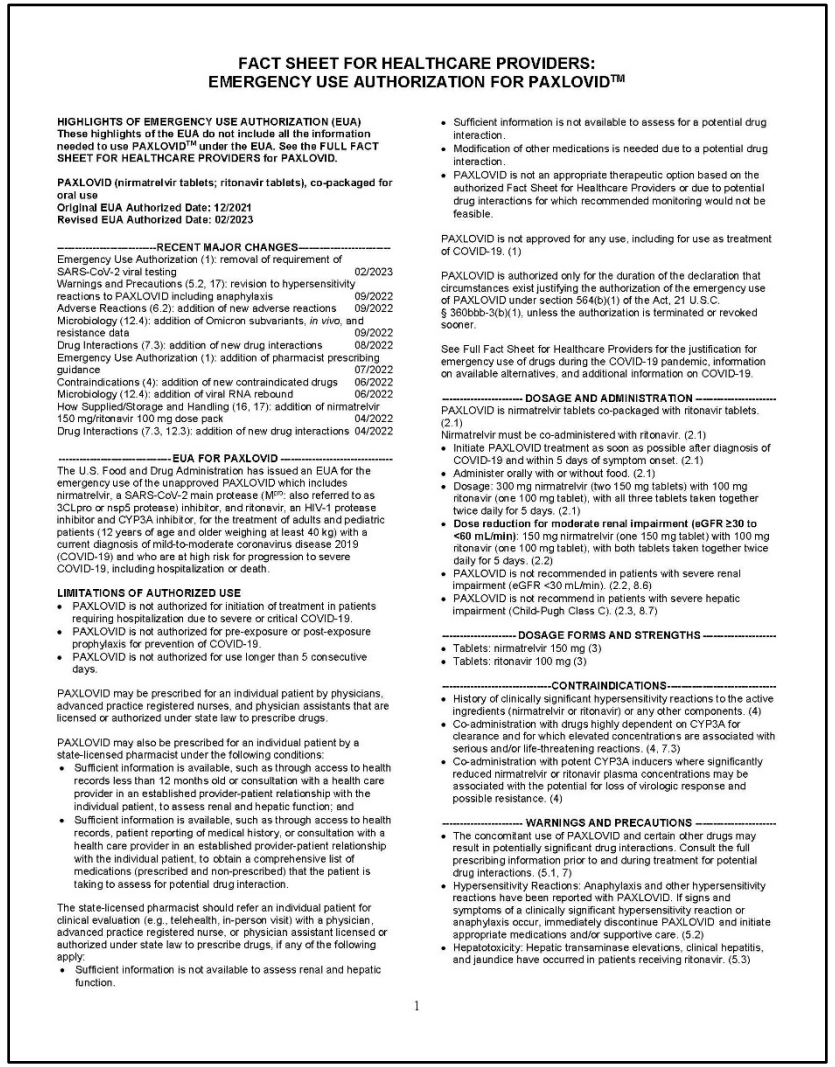
PAXLOVID

- Oral nirmatrelvir tablets co-packaged with ritonavir tablets
  - **Nirmatrelvir** is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}, also known as $3CL^{pro}$ 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^{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

Initially issued December 22, 2021

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 (M^{pro}: also referred to as $3CL^{pro}$ 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.



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

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 02/2023

----------RECENT MAJOR CHANGES----------

Emergency Use Authorization (1): removal of requirement of SARS-CoV-2 viral testing	02/2023
Warnings and Precautions (5.2, 17): revision to hypersensitivity reactions to PAXLOVID including anaphylaxis	09/2022
Adverse Reactions (6.2): addition of new adverse reactions	09/2022
Microbiology (12.4): addition of Omicron subvariants, *in vivo*, and resistance data	09/2022
Drug Interactions (7.3): addition of new drug interactions	08/2022
Emergency Use Authorization (1): addition of pharmacist prescribing guidance	07/2022
Contraindications (4): addition of new contraindicated drugs	06/2022
Microbiology (12.4): addition of viral RNA rebound	06/2022
How Supplied/Storage and Handling (16, 17): addition of nirmatrelvir 150 mg/ritonavir 100 mg dose pack	04/2022
Drug Interactions (7.3, 12.3): addition of new drug interactions	04/2022

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

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: 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.

LIMITATIONS OF AUTHORIZED USE

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

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

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

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

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

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

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.2)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.2, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.3, 8.7)

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

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

----------CONTRAINDICATIONS----------

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

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

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hypersensitivity Reactions: Anaphylaxis and other hypersensitivity reactions have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care. (5.2)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.3)

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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.

3. 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.

Overview of the Day

- Applicant Presentations
- FDA Presentations
- Lunch
- Clarifying Questions
- Open Public Hearing
- Charge to the Committee
- Questions to the Committee/Committee Discussion

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Antimicrobial Drugs Advisory Committee Meeting

March 16, 2023

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

U.S. FOOD & DRUG ADMINISTRATION

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
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  - 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

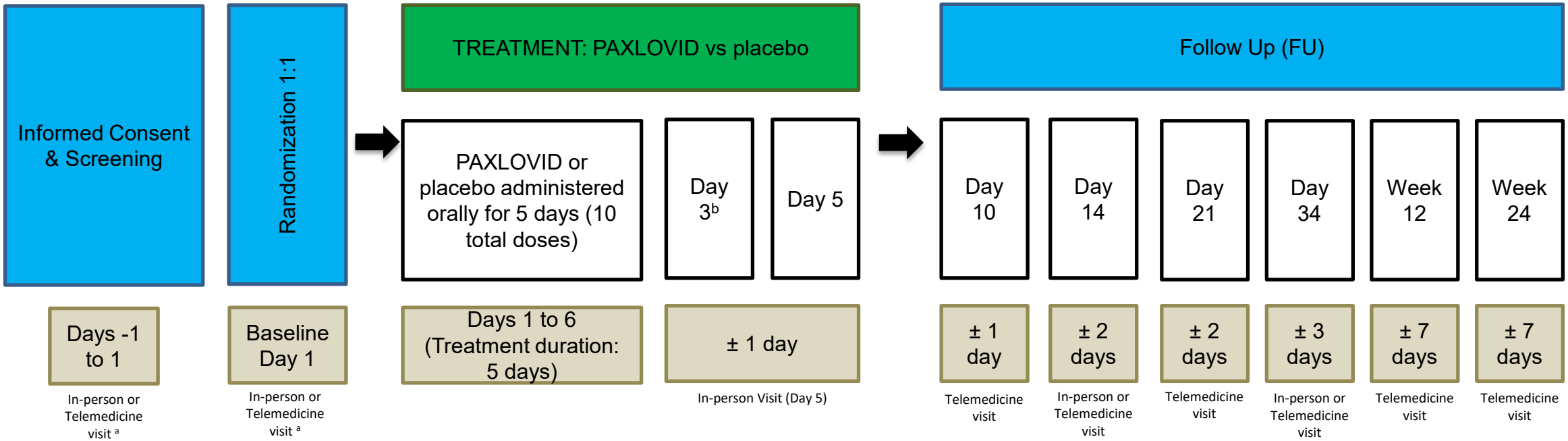
PAXLOVID Pivotal Trial

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

PAXLOVID Supportive Trials

Title	Design	Population	PAXLOVID Dose	Primary Endpoint	Time-Frame of Enrollment and Variants of Concern
Supportive Trials					
EPIC-SR	Phase 2/3 , double blind, placebo-controlled (1:1) treatment trial	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)	300/100 mg q12h x 5 days	Time to sustained alleviation of all targeted signs/symptoms through Day 28	August 2021 – November 2021 (interim analysis) Variant of concern: Delta March 2022 – June 2022 (re-opened) Variant of concern: Omicron
EPIC-PEP	Phase 2/3 , double blind, placebo-controlled (1:1:1) post-exposure prophylaxis trial	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)	300/100 mg q12h x 5 days or 10 days	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	September 2021 – March 2022 Variants of concern: Delta and Omicron

EPIC-HR Study Schema



[a] The baseline and screening visits may be a combination of in-person and telemedicine visits.
[b] The Day 3 visit must be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required

- **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 (mITT1[a])

	PAXLOVID (N=977)	Placebo (N=989)
Primary endpoint[b]: COVID-19 related hospitalization or death from any cause through Day 28, n (%)	9 (0.9%)	64 (6.5%)
COVID-19 related hospitalization through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause mortality through Day 28, %	0	12 (1.2%)

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

Trial	Population	No. of Subjects Who Received PAXLOVID
Primary Safety Data		
EPIC-HR	Unvaccinated adult outpatients with COVID-19 who are at high risk for progression to severe disease	5-day: 1038
Supportive Safety Data		
EPIC-SR	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	5-day: 540
EPIC-PEP	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	5-day: 912 10-day: 911
Total		**3401[a]**

[a]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

	EPIC-HR		EPIC-SR		EPIC-PEP		
Event Category	**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 (%)**
SAE	18 (1.7)	71 (6.7)	8 (1.5)	11 (2.1)	3 (0.3)	1 (0.1)	2 (0.2)
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)
Any AE	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)

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

Most Frequent (≥1% in EPIC-HR) All-Causality AEs

	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 (%)**
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)

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

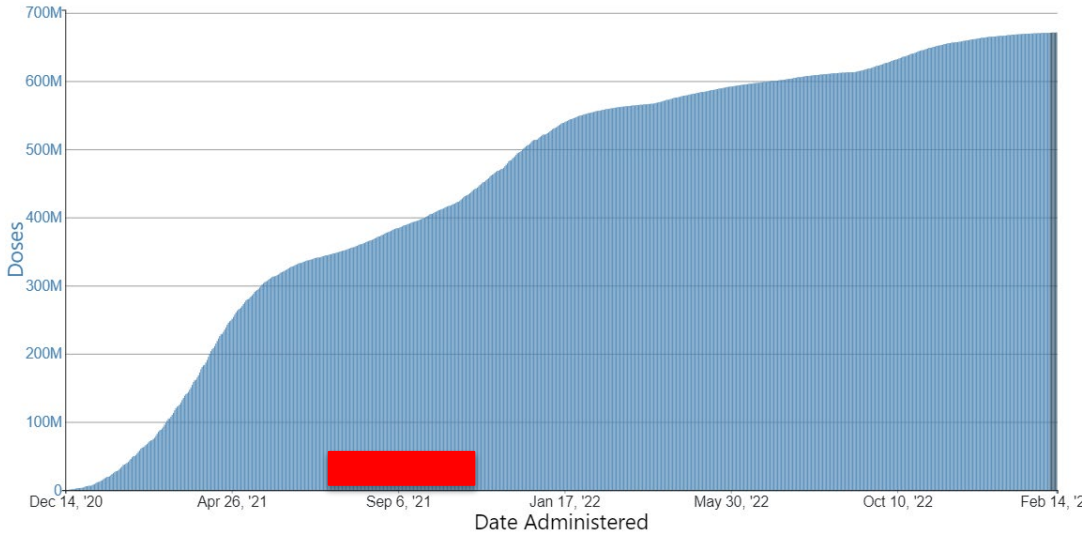
U.S. FOOD & DRUG ADMINISTRATION

Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Had a Prior SARS-CoV-2 Infection

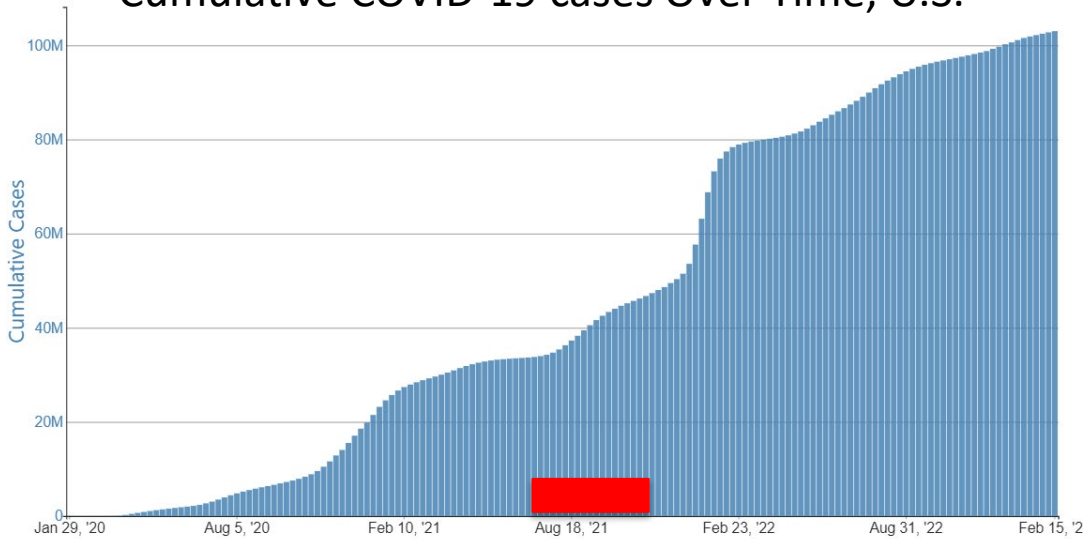
Stephanie Troy, MD, Clinical Reviewer
Jie Cong, PhD, Statistical Reviewer
Patrick Harrington, PhD, Clinical Virology Reviewer
Natasha Pratt, PhD, Epidemiology Reviewer
Jiwei He, PhD, Statistical Reviewer
Thamban Valappil, PhD, Supervisory Mathematical Statistician
Jules O'Rear, PhD, Clinical Virology 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

Cumulative Vaccine Doses Administered Over Time, U.S.



Cumulative COVID-19 cases Over Time, U.S.



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])

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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)

- 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, 2023[1]
  - Completed primary series[2]: **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).*

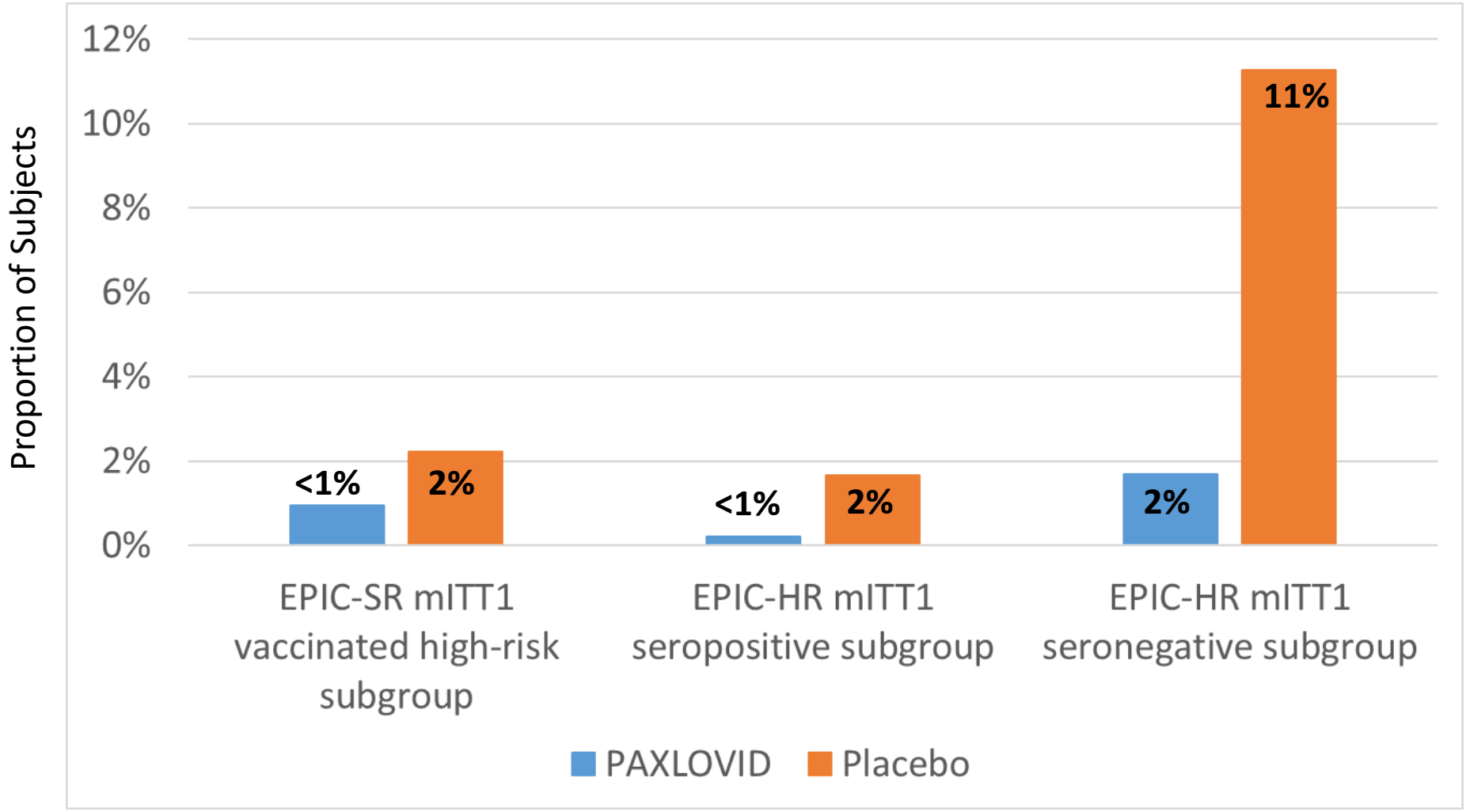
1. Information taken from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-count-pop12 on February 16, 2023
2. **92%** all adults and **95%** adults ≥65-years-old in the U.S. have received ≥1 vaccine dose

Benefit in Subjects With Baseline SARS-CoV-2 Immunity: Clinical Trial Data

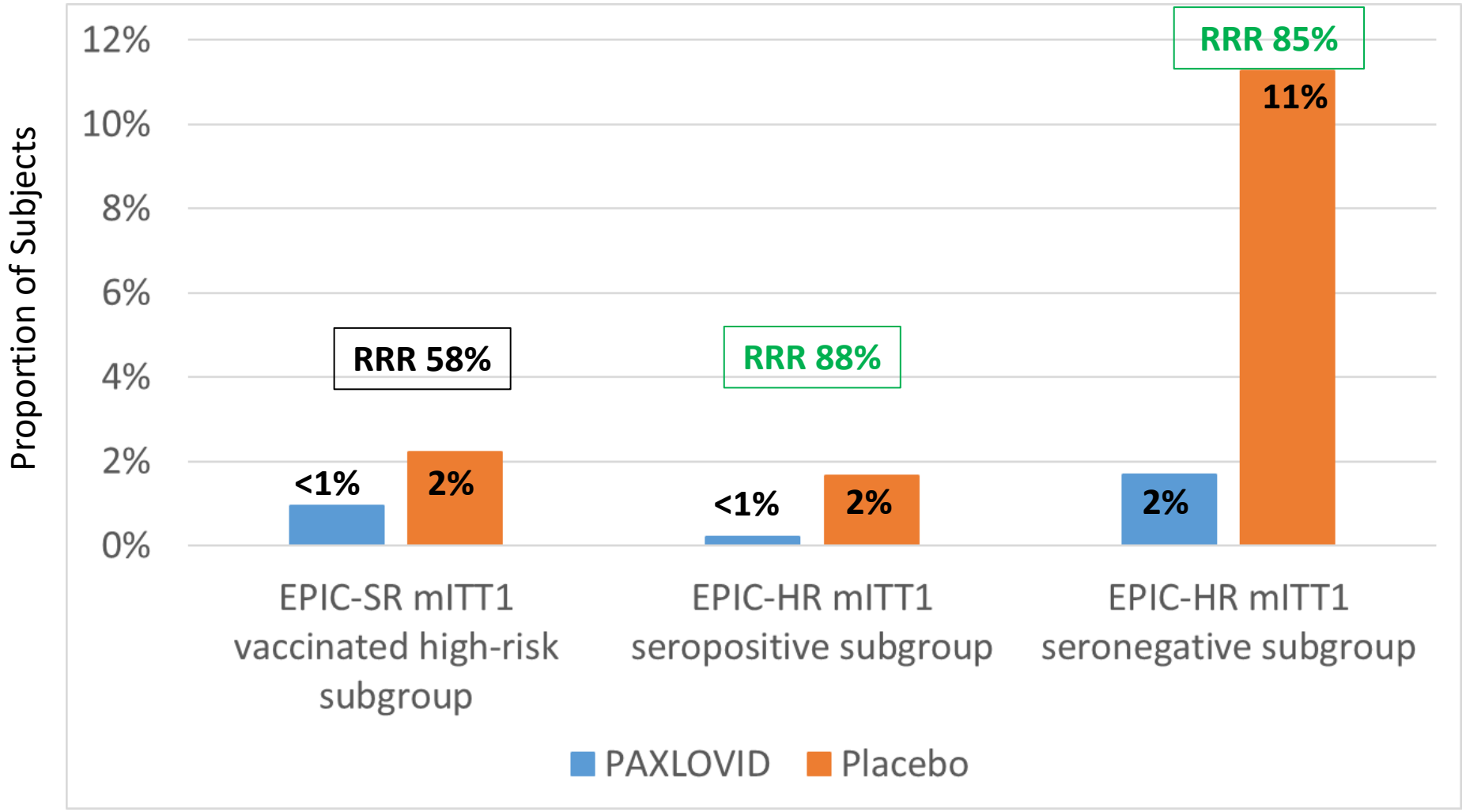
Data Analyzed in Following Subgroups:

- **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



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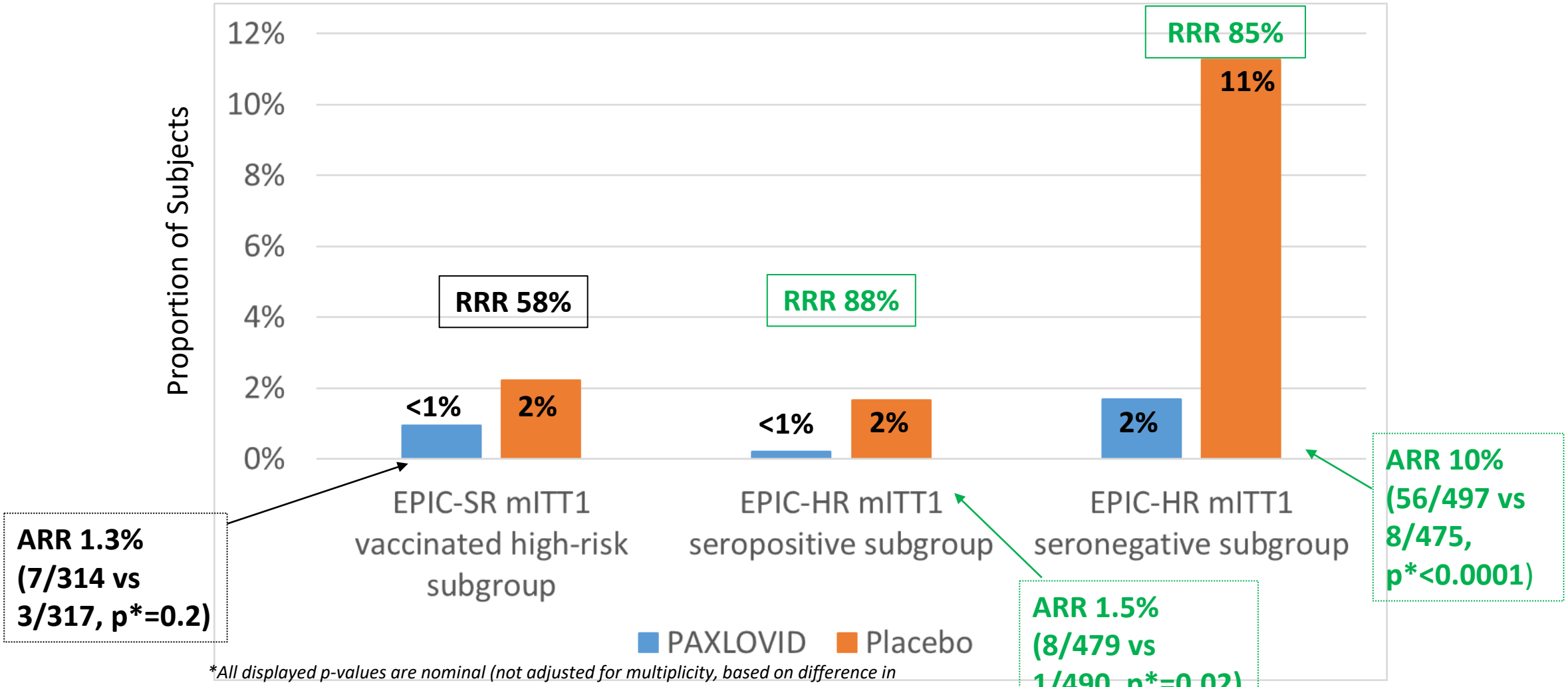
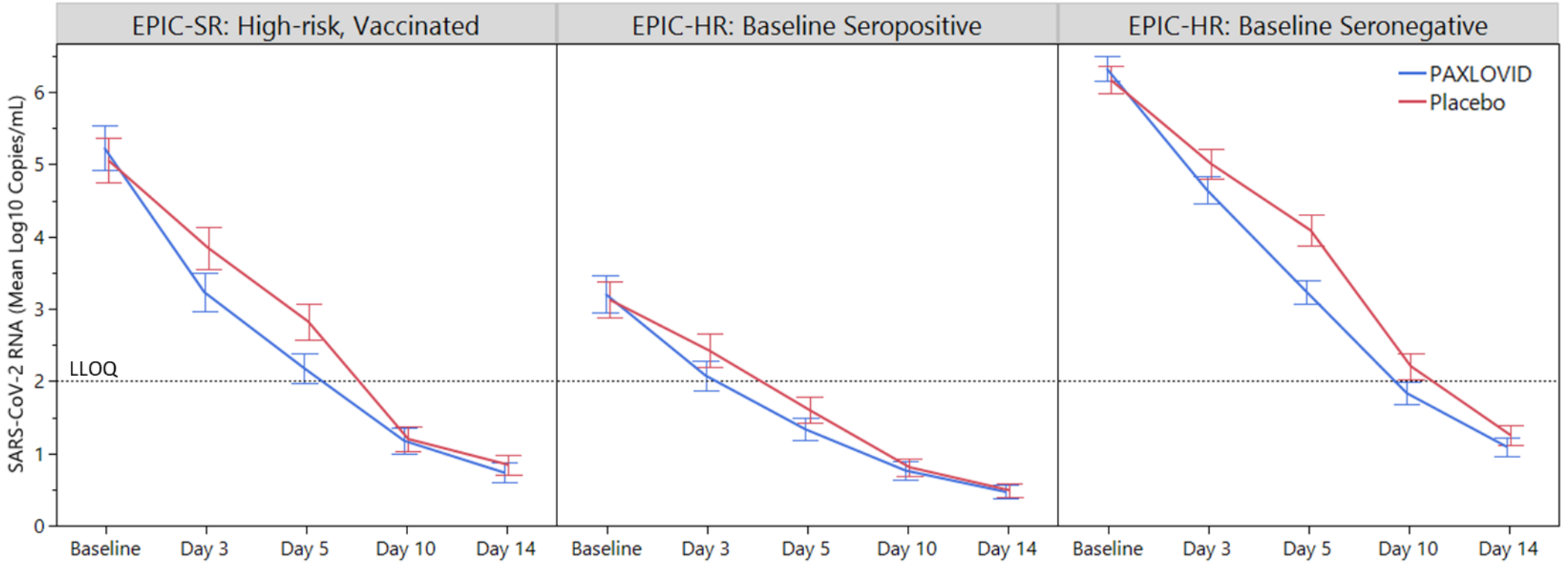


All displayed p-values are nominal (not adjusted for multiplicity, based on difference in estimated proportions using the Kaplan-Meier Method)

SARS-CoV-2 RNA Levels Over Time



Abbreviations: LLOQ, lower limit of quantification

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.

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.

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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^{pro} Protease With Natural Amino Acid Polymorphisms

M^{pro} Polymorphism*	Cumulative Frequency (as of 11/30/2022)	Geomean K_i Fold-Change
P132H	**45.5%**	**0.7**
K90R	1.4%	1.2
L89F	1.2%	2.1
T169S	0.5%	1.1
P108S	0.2%	2.9
A260V	0.2%	0.6
G15S	0.2%	1.6
L75F	0.2%	0.3
K88R	0.2%	0.5
T21I	0.1%	1.6

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

- In biochemical assays, nirmatrelvir retained activity (K_i fold-change <3) against recombinant SARS-CoV-2 M^{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

SARS-CoV-2 Variant	M^{pro} Polymorphism(s)	Geomean EC_{50} (nM)	EC_{50} Value Fold-Change	Geomean EC_{90} (nM)	EC_{90} Value Fold-Change
USA-WA1/2020	N/A	70	N/A	211	N/A
Omicron BA.2	P132H	65	0.9	132	0.6
Omicron BA.2.12.1	P132H	40	0.6	114	0.5
Omicron BA.4	P132H	39	0.6	98	0.5
Omicron BA.5	P132H	44	0.6	178	0.8

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

- 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 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^{pro} Protease and Cleavage Sites

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

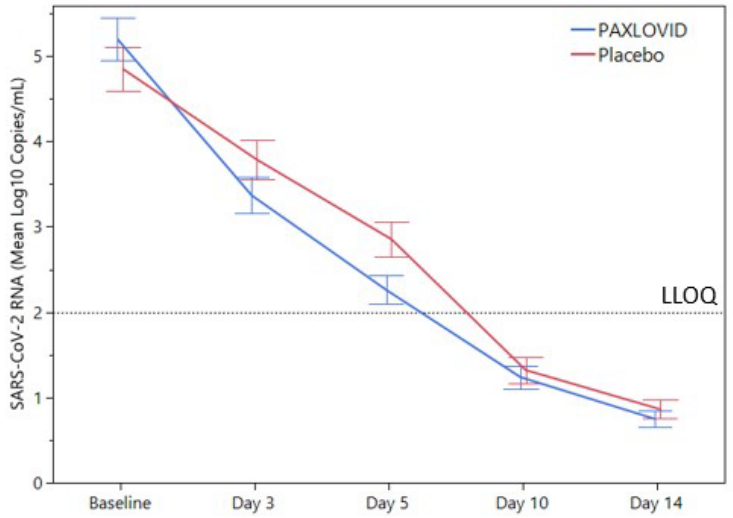
- Only 10 M^{pro} protease polymorphisms had a cumulative frequency ≥0.1% (range: 0.1-1.4%, excluding P132H); nirmatrelvir retained activity against M^{pro} enzymes with these polymorphisms in biochemical assays (K_i fold-change <3)

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

- Overall, these analyses demonstrate that SARS-CoV-2 M^{pro} protease and cleavage site sequences are highly conserved and that nirmatrelvir is expected to retain activity against Omicron variants

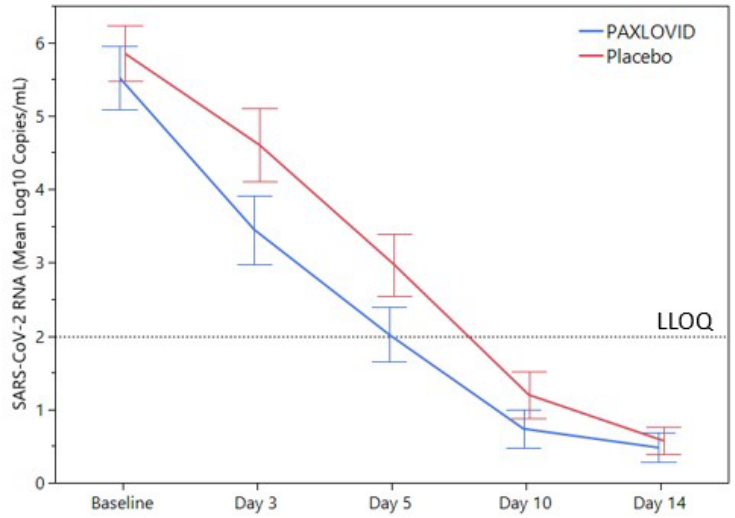
Effect of PAXLOVID on SARS-CoV-2 RNA Shedding

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)

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

U.S. FOOD & DRUG ADMINISTRATION

Impact of PAXLOVID on COVID-19 Rebound

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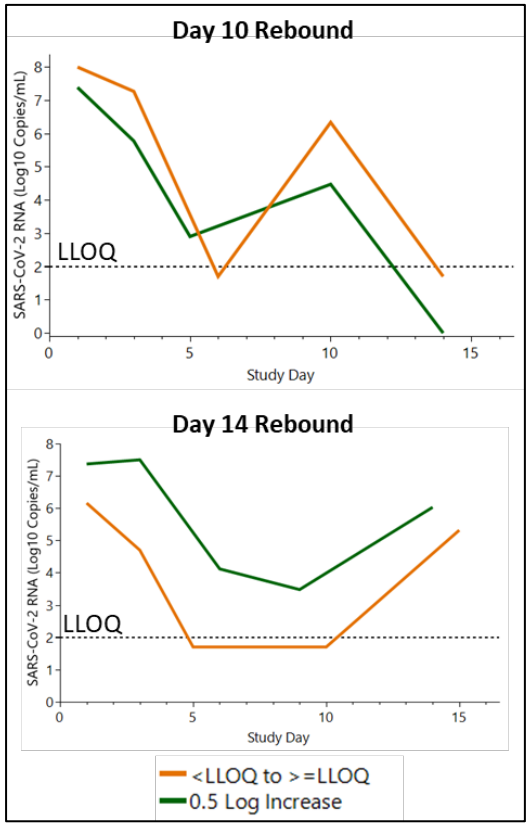
Stephanie Troy, MD, Clinical Reviewer
Yan Li, PhD, Epidemiology Reviewer
Jules O'Rear, PhD, Clinical Virology Team Leader
Thamban Valappil, PhD, Supervisory Mathematical Statistician
Natasha Pratt, PhD, Epidemiology Team Leader
Sarah Connelly, MD, Cross-Discipline Team Leader

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

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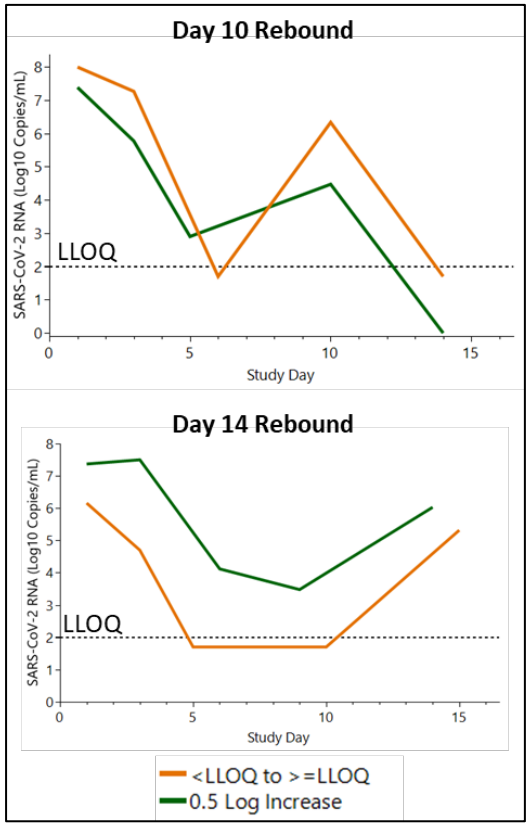

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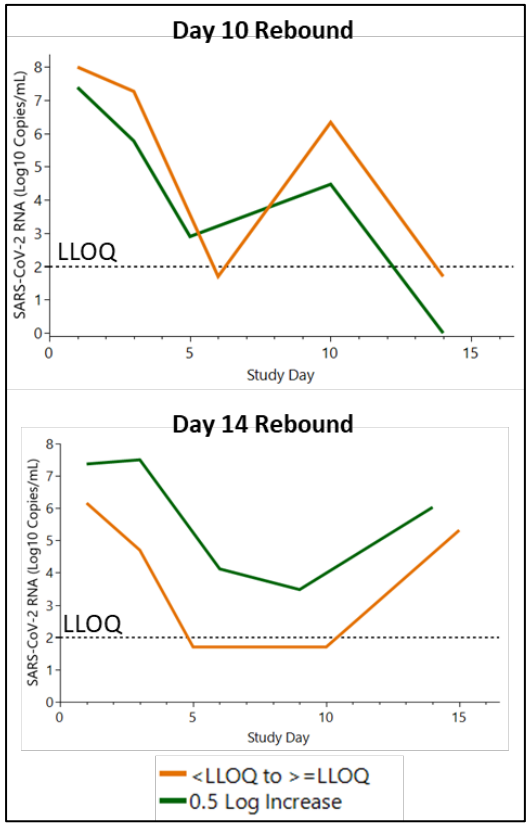

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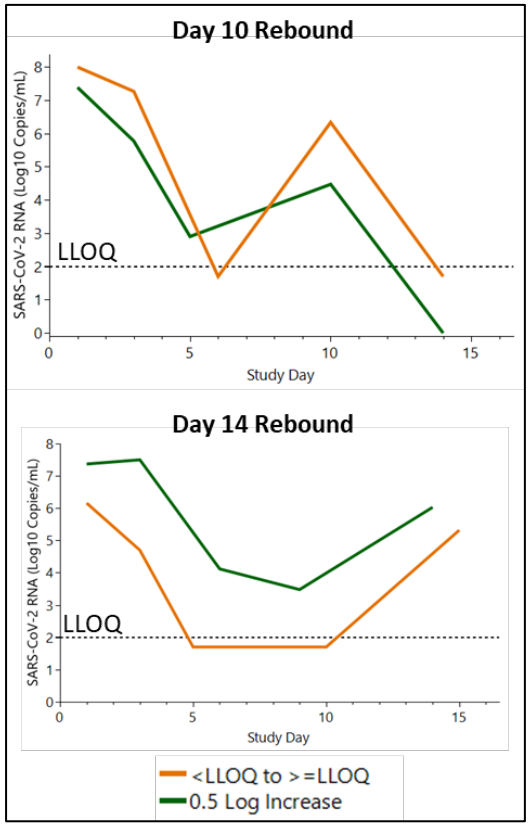

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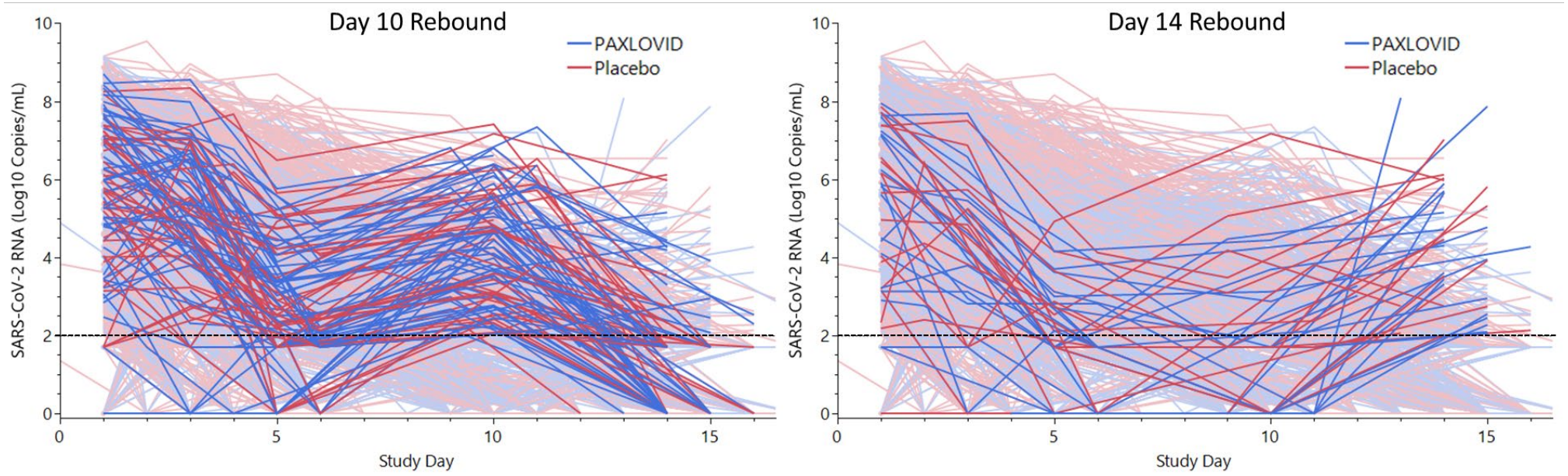
Viral RNA Rebound in EPIC-HR

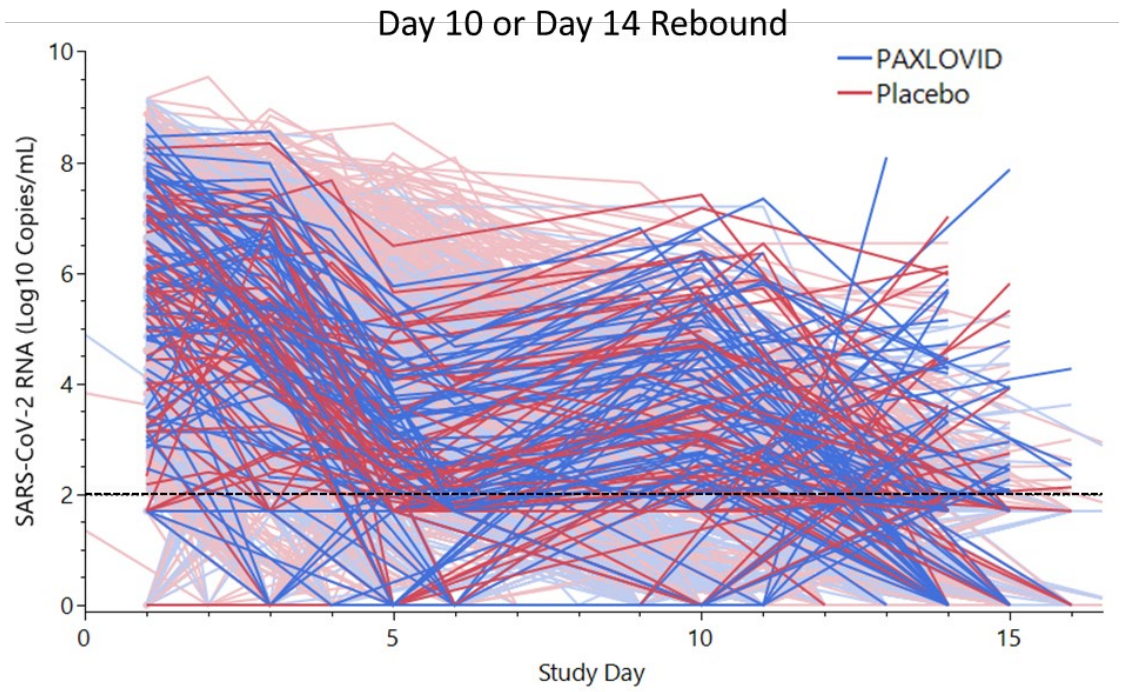


PAXLOVID: 6.6% (57/865)
Placebo: 4.7% (40/856)
p=0.09*

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



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

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

Viral RNA Rebound in EPIC-HR:

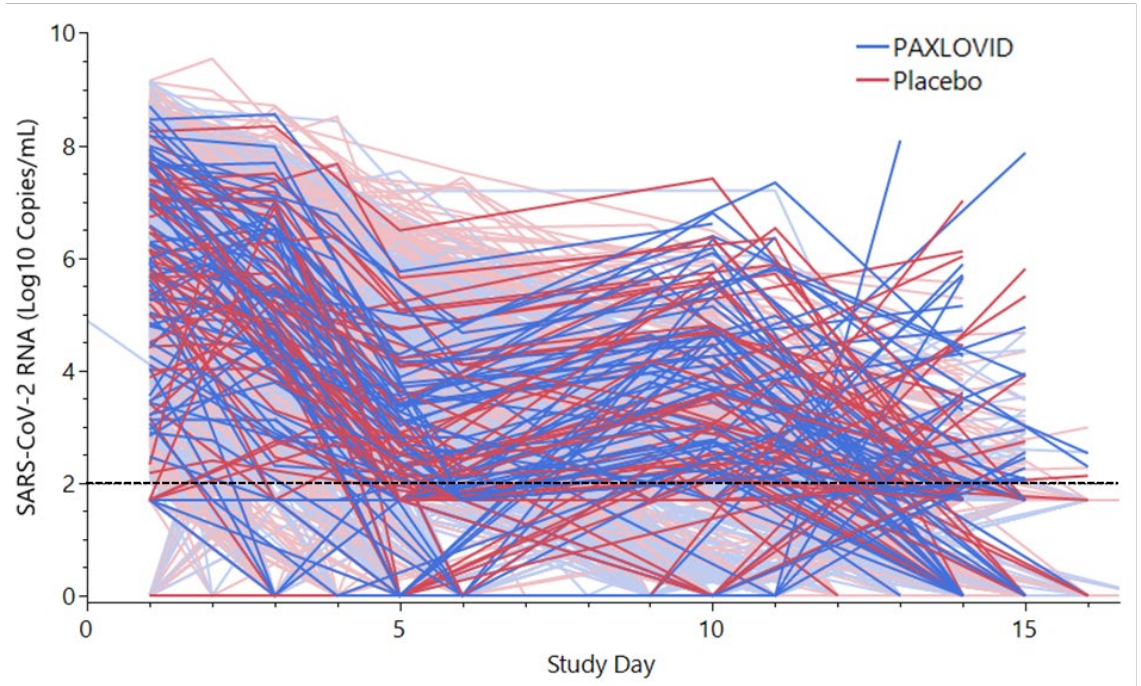
Caution in Interpretation of Viral RNA Rebound Rates

- "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 $\log_{10}$ copies/mL decline from BL to Day 5)

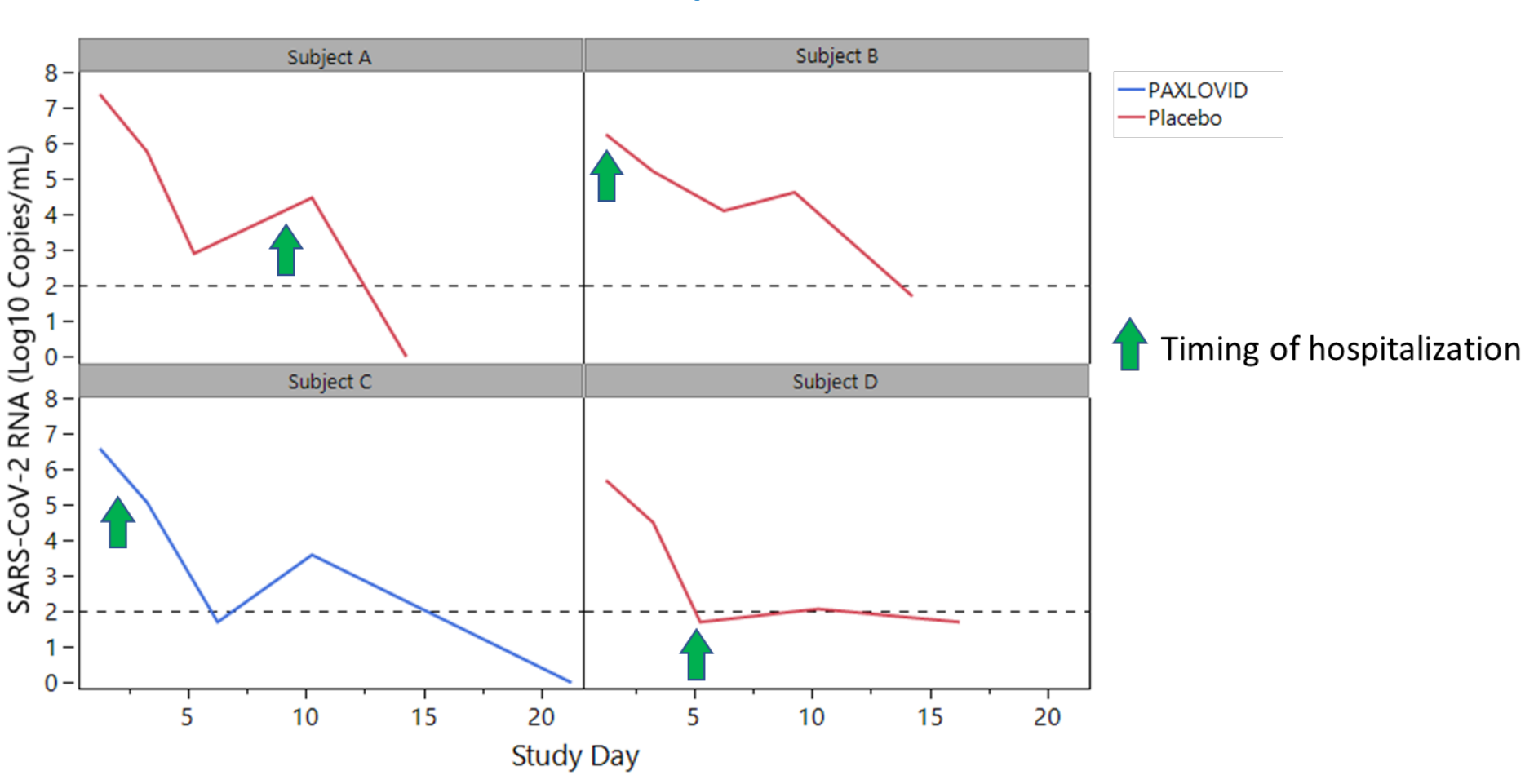


PAXLOVID: 8.1% (69/849)
Placebo: 6.5% (50/772)
p=0.22*

*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:

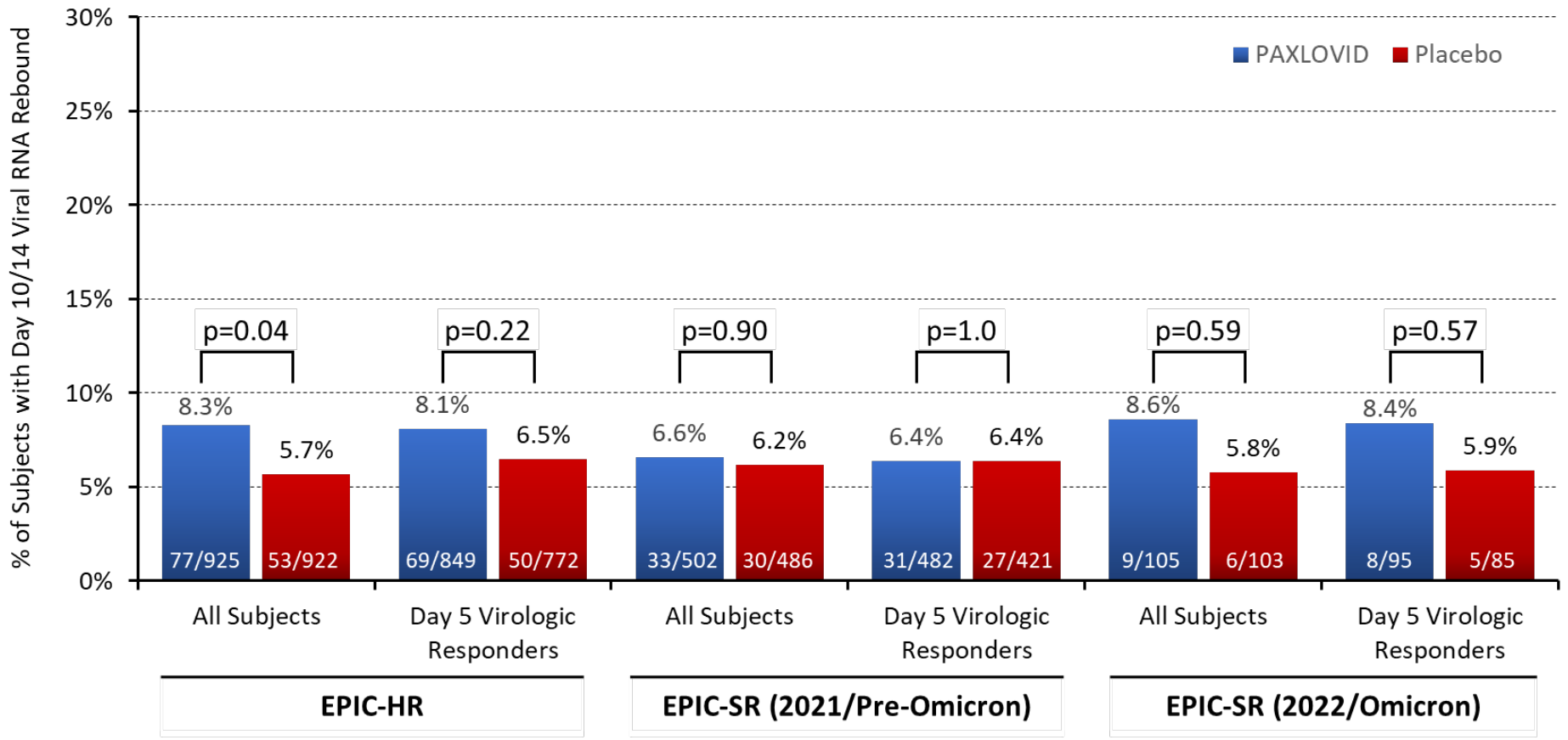
4 Subjects w/Hospitalization or Death (n=1 PAXLOVID, n=3 Placebo; no deaths)

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^{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 [$TCID_{50}$])
  - 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 ($TCID_{50}$) 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.

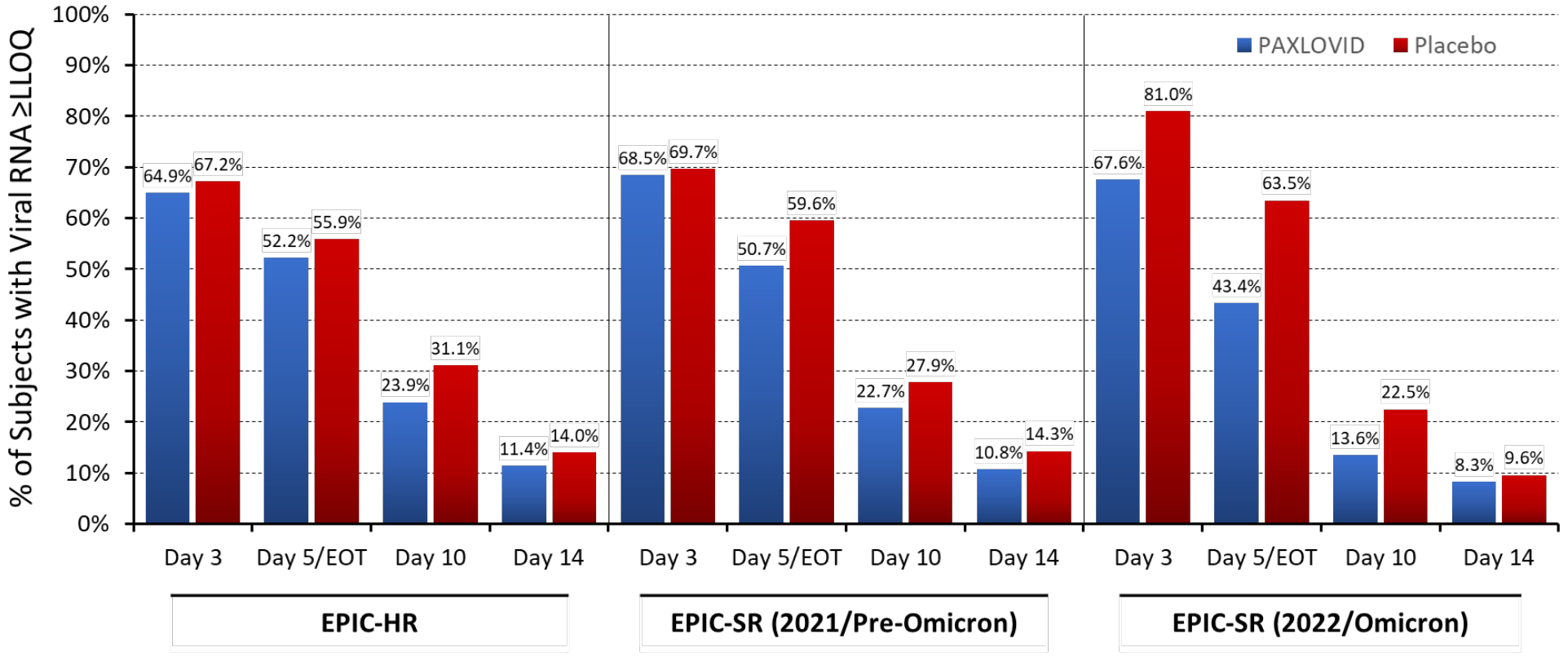
Viral RNA Rebound Rates (Day 10 or Day 14) Across EPIC-HR and EPIC-SR



*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



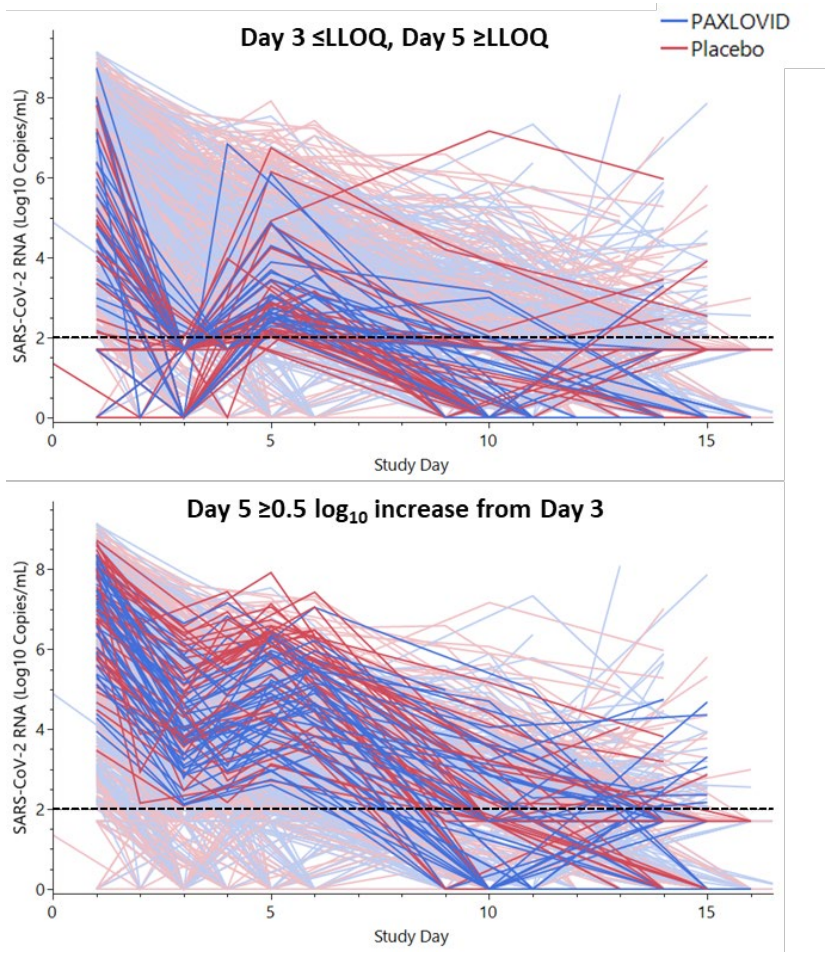
At <u>all</u> analysis timepoints, relative to Placebo recipients, PAXLOVID recipients were less likely to have viral RNA ≥LLOQ, regardless of any differences in rebound rates from Day 5 to Days 10/14.

Viral RNA "Rebound" On-Treatment

EPIC-HR

	PAXLOVID	Placebo
On-treatment Viral RNA "Rebound"*	**11.3% (77/680)**	**12.5% (74/594)**
Post-treatment (D10/D14) Viral RNA Rebound, Day 5 Responders	8.1% (69/849)	6.5% (50/772)

*Day 3 Viral RNA Response (<LLOQ or ≥1 $\log_{10}$ copies/mL from BL to Day 3) AND
- Day 3 ≤LLOQ, followed by Day 5 ≥LLOQ, OR
- Day 3 ≥LLOQ, followed by Day 5 ≥0.5 $\log_{10}$ increase from Day 3



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 ≥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

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- **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

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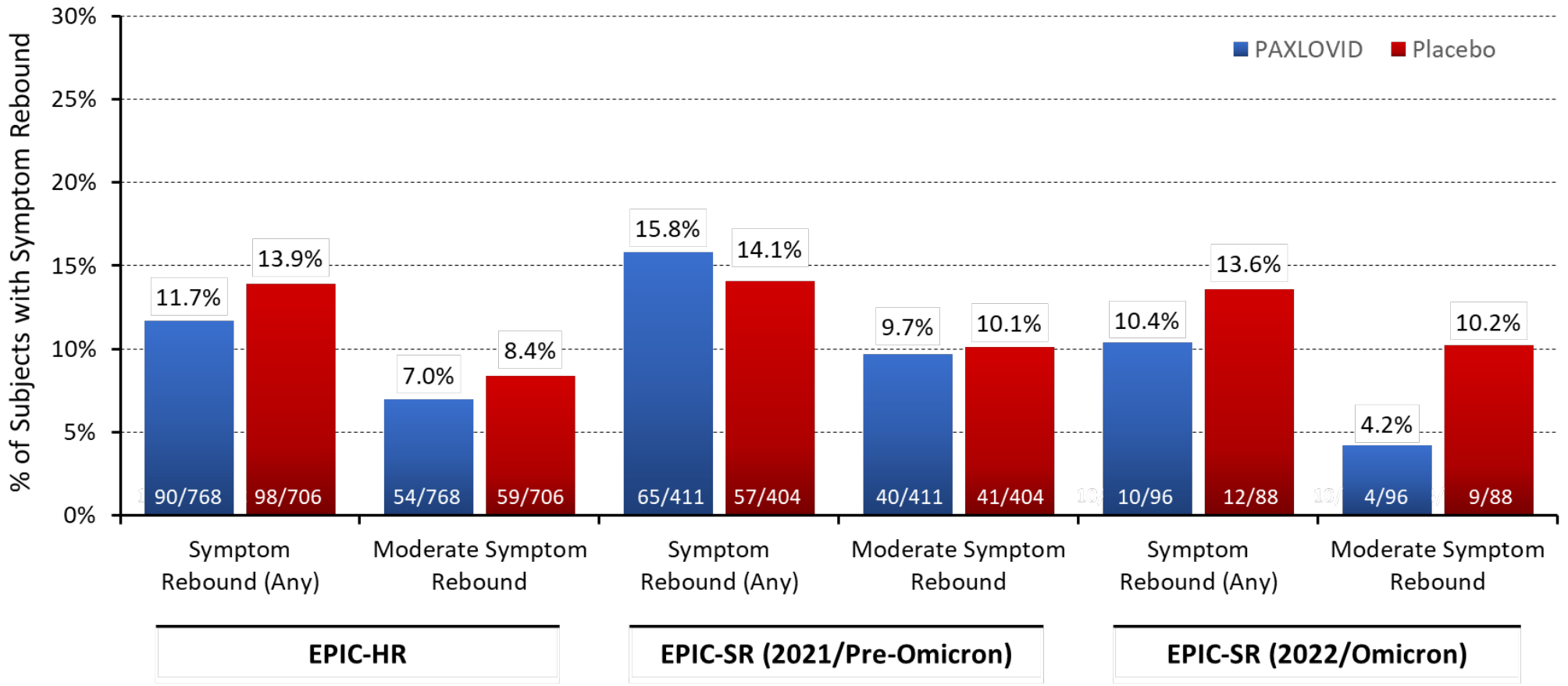
Symptom Rebound Through Day 28



Combined Symptom + Viral RNA Rebound

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**

[a] Percentage over total subjects.
[b] 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.

U.S. FOOD & DRUG ADMINISTRATION

Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients

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Ye Xiong, PhD, Pharmacometrics Reviewer
Cristina Miglis, PharmD, MS, Clinical Pharmacology Reviewer
Patrick Harrington, PhD, Clinical Virology Reviewer
Jiang Liu, PhD, Pharmacometrics Team Leader
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Mario Sampson, PharmD, Clinical Pharmacology Team Leader
Jules O'Rear, PhD, Clinical Virology Team Leader
Sarah Connelly, MD, Cross-Discipline Team Leader

Optimal Duration of PAXLOVID in Immunocompromised Patients

- 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.)

1. Lee, CY, et al., 2022, Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies, Cancer Discov, 12(1):62-73.

PAXLOVID in Immunocompromised Patients: Available Clinical Data

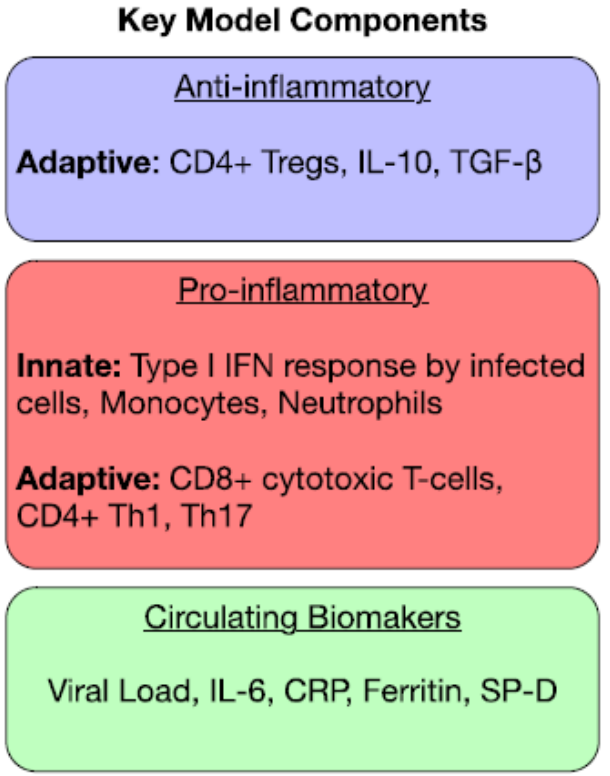
- EPIC-HR: <1% of subjects (n=13) were classified as having immunosuppression
  - None met the primary endpoint (hospitalization/death)
  - None of the six randomized to PAXLOVID had evidence of increased SARS-CoV-2 RNA levels after treatment was stopped on Day 5
- >20 severely immunosuppressed patients 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[1]
  - **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.*

1. Ford, ES, et al., 2022, Successful treatment of prolonged, severe COVID-19 lower respiratory tract disease in a B-cell ALL patient with an extended course of remdesivir and nirmatrelvir/ritonavir, Clin Infect Dis.; Trottier, CA, et al., 2022, Dual antiviral therapy for persistent COVID-19 and associated organizing pneumonia in an immunocompromised host, Clin Infect Dis.

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

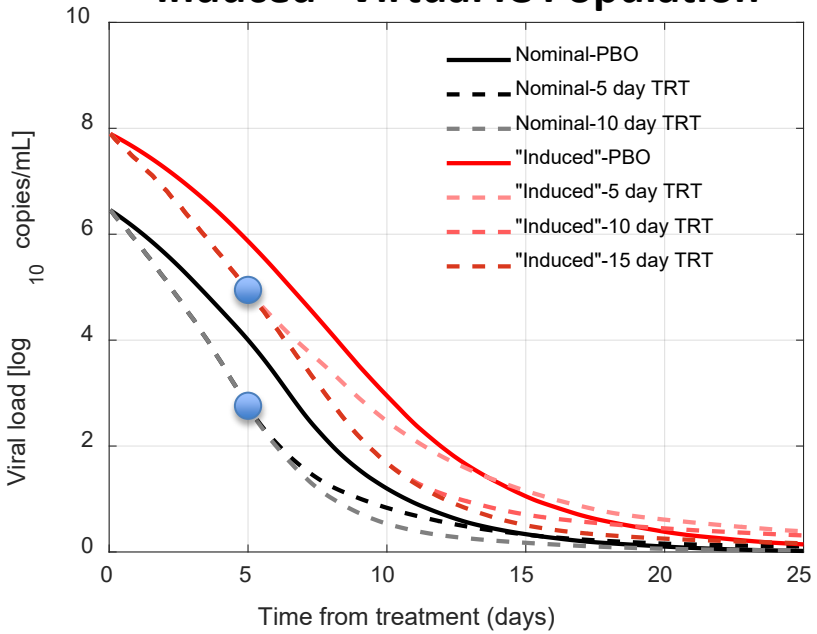
- Simulation for general population, further calibrated by EPIC-HR data
- Simulation for immunocompromised (IC) population: Two virtual IC populations were generated to assess viral RNA suppression with various dosing periods, in comparison with 5-day dosing using:
  - "induced": 50% effect of Type I IFN and CD8+ T cells
  - "resembling": top 85th viral shedding duration

Graph from Applicant's EPIC-IC QSP model summary

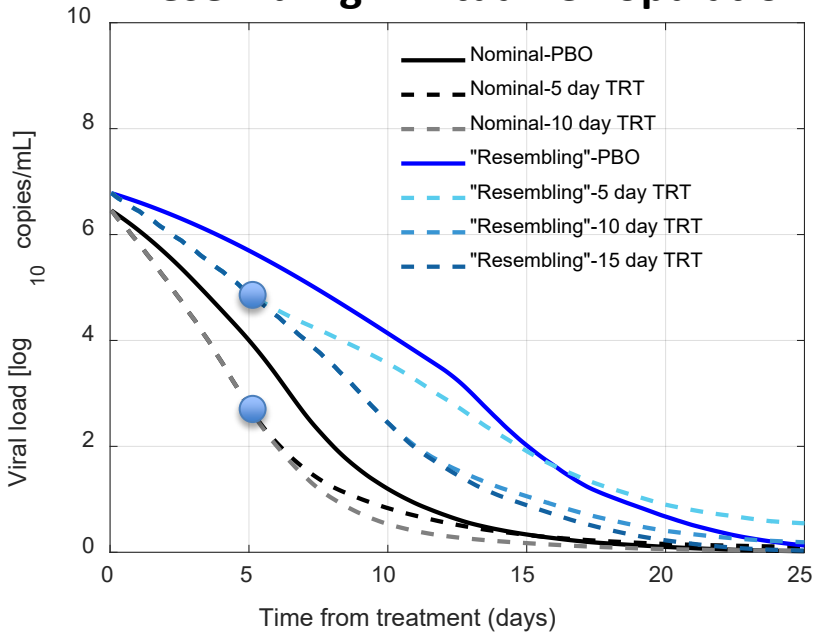
QSP Model to Support Studying Longer Treatment Durations in IC Population in Clinical Trials

- "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.

Different Treatment Durations: "Induced" Virtual IC Population



Different Treatment Durations: "Resembling" Virtual IC Population



Summary graph of EPIC-IC QSP model

Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients: Conclusion

- 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

U.S. FOOD & DRUG ADMINISTRATION

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

Serious Adverse Reactions Due to DDIs

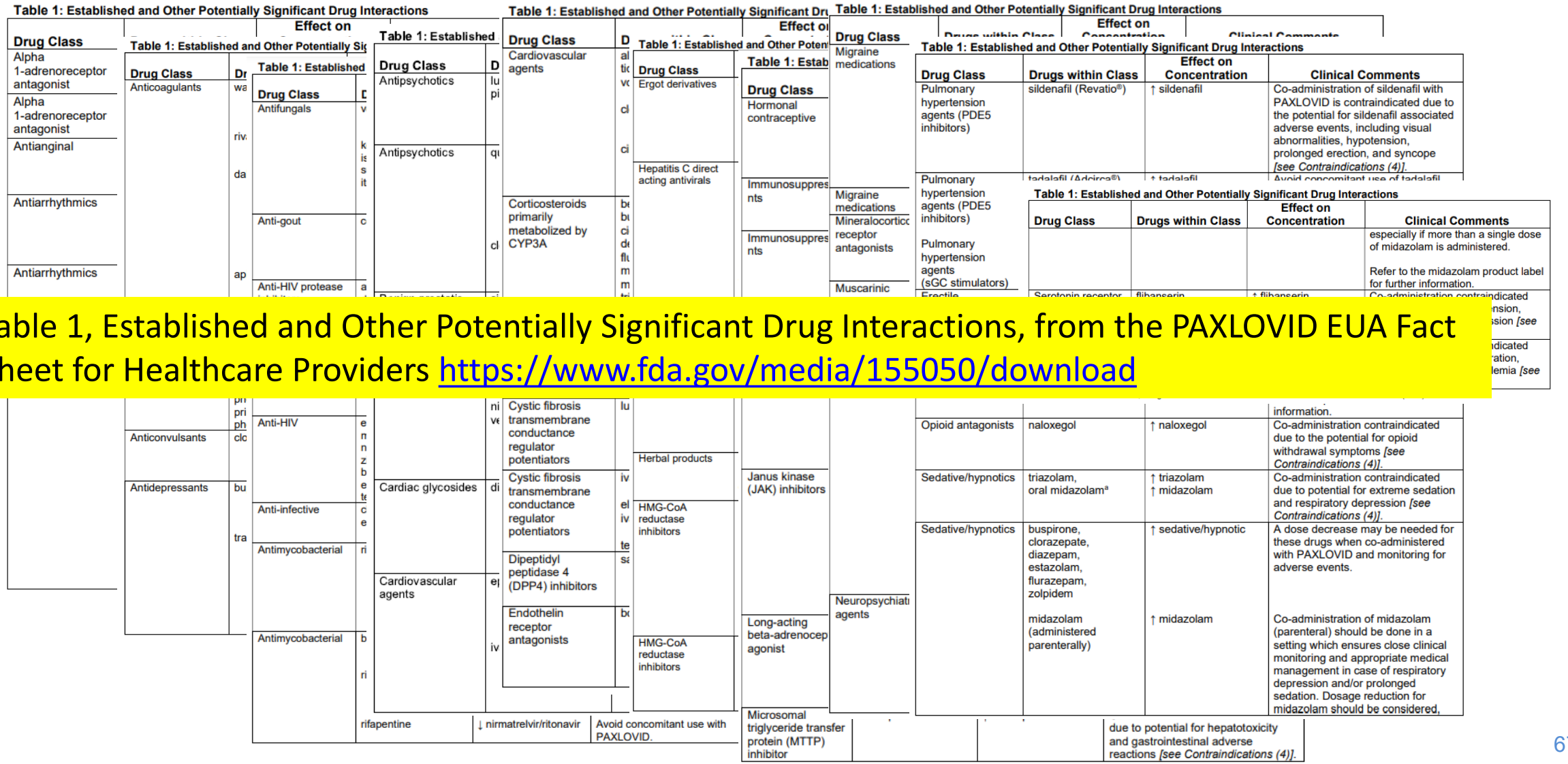
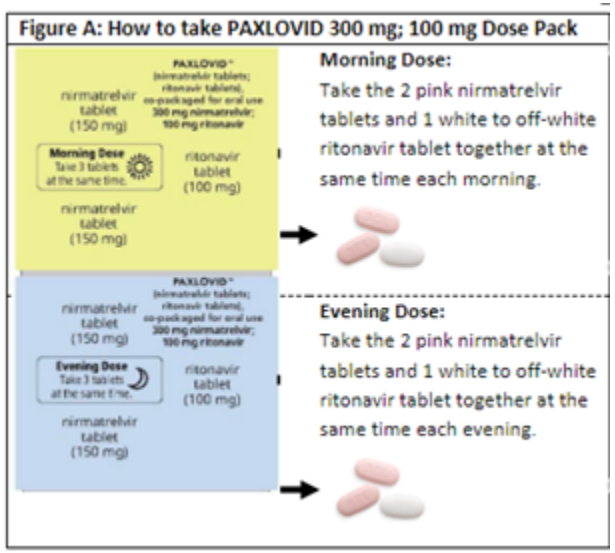


Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors) Pulmonary hypertension agents (sGC stimulators)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered,

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

	COVID-19 patients 65+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment		COVID-19 patients 50+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment		PAXLOVID users	
Medicare (12/22/2021-9/10/2022)	**Count**	**%**	**Count**	**%**	**Count**	**%**
Total N	*1,829,342*	*100.0%*	*1,844,062*	*100.0%*	*383,779*	*100.0%*
Any DDI drugs	**1,227,485**	**67.1%**	**1,234,817**	**67.0%**	**253,924**	**66.2%**
Other*	781,883	42.7%	787,613	42.7%	145,537	37.9%
Avoid Concomitant Use	715,805	39.1%	717,679	38.9%	160,335	41.8%
Contraindicated	215,581	11.8%	216,960	11.8%	40,192	10.5%
VA (01/01/2022-10/31/2022)	**Count**	**%**	**Count**	**%**	**Count**	**%**
Total N	*169,235*	*100.0%*	*206,879*	*100.0%*	*30,360*	*100.0%*
Any DDI drugs	**110,370**	**65.2%**	**117,242**	**56.7%**	**18,790**	**61.9%**
Other*	78,800	46.6%	84,000	40.6%	13,230	43.6%
Avoid Concomitant Use	68,434	40.4%	71,186	34.4%	11,423	37.6%
Contraindicated	15,218	9.0%	15,839	7.7%	1,995	6.6%

*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)

PAXLOVID DDI drug	Recommended Action for DDI	COVID-19 patients 65+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment		COVID-19 patients 50+ yrs or with high-risk comorbidities, no severe renal/hepatic impairment	
		Count	%	Count	%
Total N		*169,235*	*100.0%*	*206,879*	*100.0%*
Any DDI drugs		**110,370**	**65.2%**	**117,242**	**56.7%**
ATORVASTATIN	Avoid Concomitant Use	39321	23.2%	40861	19.8%
AMLODIPINE	Other*	24,834	14.7%	25,280	12.2%
TAMSULOSIN	Avoid Concomitant Use	19512	11.5%	20147	9.7%
SILDENAFIL	Other	14,414	8.5%	15,876	7.7%
FLUTICASONE	Other	13,867	8.2%	14,940	7.2%
ROSUVASTATIN	Avoid Concomitant Use	10877	6.4%	11290	5.5%
TRAZODONE	Other	10,099	6.0%	10,934	5.3%
SIMVASTATIN	Contraindicated Drug	9,045	5.3%	9,426	4.6%
APIXABAN	Other	7,806	4.6%	7,870	3.8%
SALMETEROL	Avoid Concomitant Use	7,376	4.4%	-	-
BUPROPION	Other	-	-	8,041	3.9%

*Other includes actions like dose modification, laboratory monitoring, and clinical monitoring.

Drug Utilization Top Specialties

	N	%
Total Paxlovid Prescriptions	**8,427,383**	**100.0%**
Family Practice/General Practice/Internal Medicine	6,271,340	74.4%
Emergency Medicine	605,452	7.2%
Nurse Practitioner	219,455	2.6%
Pediatrics	192,458	2.3%
Geriatrics	92,538	1.1%
Pharmacist	405	<0.1%
All Other Specialties	543,741	6.5%
Unknown	501,994	6.0%

Source: Symphony Health Metys™. Week ending December 31, 2021 - Week ending January 13, 2023. Data extracted January 2023.

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.

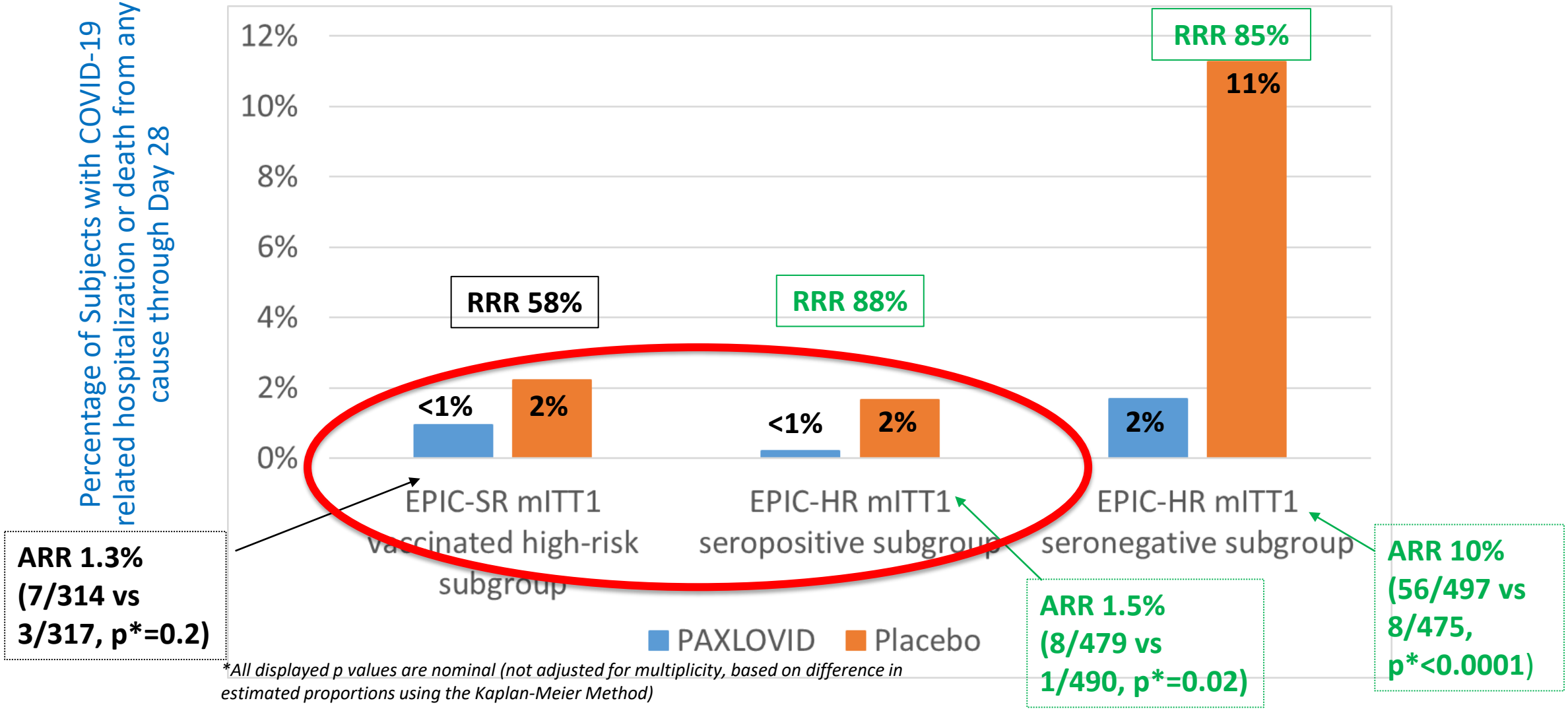
Reports of Serious Adverse Events Due to PAXLOVID DDIs That Are Included in Labeling*

- 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

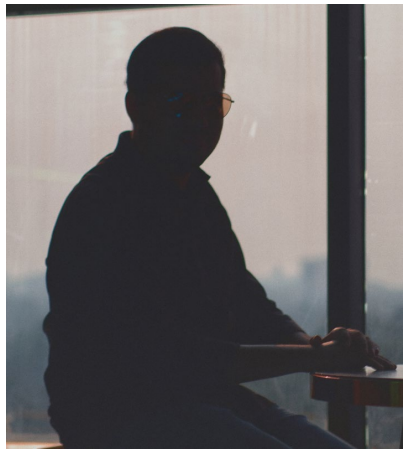
Reminder: PAXLOVID Benefit in 2023 When Most People in the U.S. Have Some baseline SARS-CoV-2 Immunity



*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 still[1]:
    - 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.

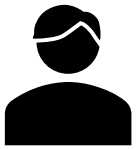
1. https://covid.cdc.gov/covid-data-tracker/#datatracker-home, accessed January 29, 2023.

Top picture taken from Microsoft 365 Stock Images. Bottom picture taken from photo by Amrut Roul on Unsplash.

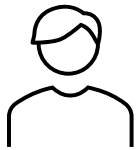
Benefit-Risk Assessment: One Family

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**

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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

NDA 217188

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.

3. 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.


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