

# Clinically Relevant Endpoints for Covid-19 and Influenza

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# Disclaimer

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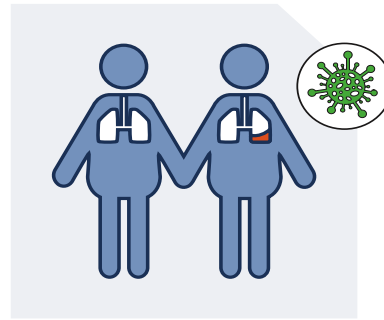
# Therapeutic interventions vary depending upon the stage of infection and patient populations



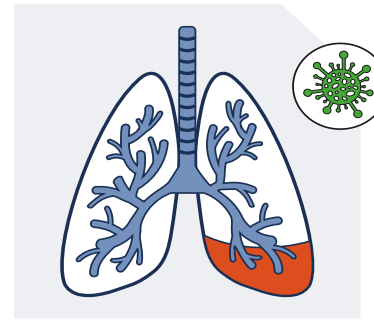
**Pre-exposure prophylaxis**  
In High Risk/  
Low Risk



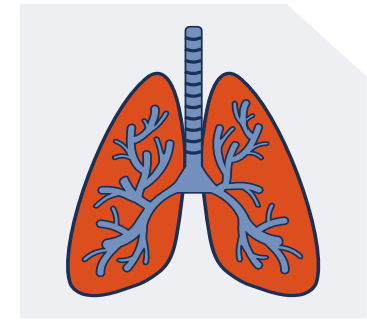
**Post-exposure prophylaxis**  
In High Risk/  
Low Risk



**Out-patient treatment**  
in High Risk/  
Standard Risk



**Hospitalized moderate/severe**



**Hospitalized (critical cases)**

# Clinical questions of interest depend on the stage of viral infection and patient population



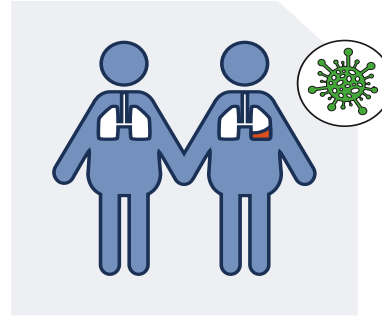
**Pre-exposure prophylaxis**  
In High Risk/  
Low Risk

- Lab confirmed infections
- Lab confirmed symptomatic infections



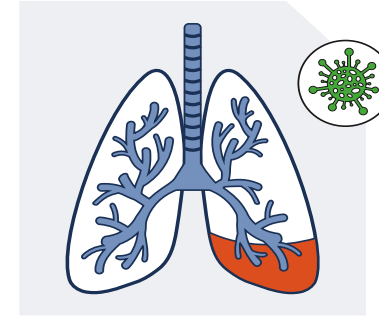
**Post-exposure prophylaxis**  
In High Risk/  
Low Risk

- Lab confirmed symptomatic infections
- Lab confirmed infections



**Out-patient treatment**  
in High Risk/  
Standard Risk

- All cause mortality
- Hospitalization
- Sustained symptom alleviation or resolution



**Hospitalized Moderate/Severe**

- All cause mortality
- Respiratory failure
- Need for mechanical ventilation
- Return to room air or baseline oxygen requirement
- Ordinal scale of multiple clinically relevant endpoints



**Hospitalized (critical cases)**

- All cause mortality
- Respiratory failure

# Choice of clinical endpoints is influenced by

- What is meaningful to
  - Patients
  - Clinicians
  - **Regulators**
  - Policy makers
- What the drug can do
  - Antivirals
  - Monoclonals
- What is feasible
  - Event rate in the population
  - Information needed to set the non-inferiority margin (for active control studies)
  - Potential to enroll adequate number of patients in a reasonable timeframe

# Some Examples...

# PAXLOVID EPIC-HR Study in high-risk patients

## Covid-19 related hospitalizations or deaths from any cause

**Table 9: COVID-19 Related Hospitalization or Death from Any Cause Through Day 28 in Non-Hospitalized Adults with COVID-19 (mITT1 Analysis Set): EPIC-HR**

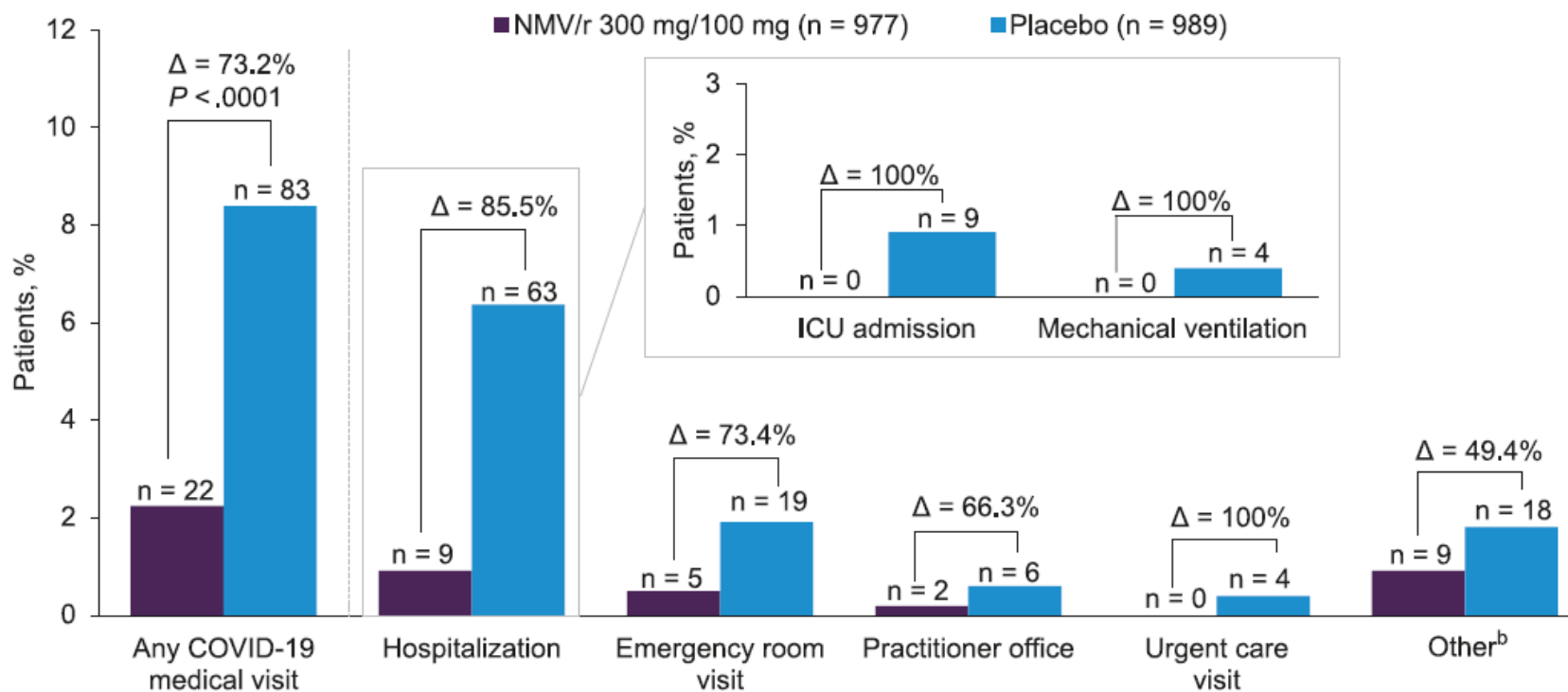
	<b>PAXLOVID (N=977)</b>	<b>Placebo (N=989)</b>
<b>COVID-19 Related Hospitalization or Death from Any Cause Through Day 28</b>		
n (%)	9 (0.9%)	64 (6.5%)
Reduction Relative to Placebo <sup>a</sup> (95% CI), %	-5.6 (-7.3, -4.0)	
COVID-19 Related Hospitalization Through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause Mortality Through Day 28 <sup>b</sup> , %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

Source: Paxlovid FDA Label

# PAXLOVID EPIC-HR Study in high-risk patients

## Covid-19 related medical visits and deaths due to any cause



**Figure 3.** COVID-19–related medical visits and deaths due to any cause<sup>a</sup> (mITT1 population). <sup>a</sup>COVID-19–related hospitalizations were assessed through day 28, whereas other categories of COVID-19 medical visits were reported through day 34 visit. <sup>b</sup>Other includes use of home healthcare services, telephone consultation, outpatient infusion center, and other. ICU, intensive care unit; mITT1, modified intent-to-treat 1; NMV/r, nirmatrelvir/ritonavir; Δ, relative risk reduction.

# PAXLOVID EPIC-HR Study in High-Risk patients

## *Median time to sustained alleviation of symptoms through Day 28*

Key Secondary End Point	PLACEBO (N = 1036)	PAXLOVID (N = 1026)
Proportion of patients who achieved sustained alleviation	72.7%	64.9%
Median time to sustained alleviation	15 days	13 days
Hazard ratio	1.27 (95% CI: 1.13, 1.41, p < 0.0001)	

Source: FDA AdCom Meeting for Paxlovid, March 16, 2023

# PAXLOVID EPIC-SR Study in standard-risk patients

## *Median time to sustained alleviation of symptoms through Day 28*

**Table 2.** Time to Sustained Alleviation of All Targeted Signs and Symptoms through Day 28.\*

Variable	Nirmatrelvir–Ritonavir (N = 654)	Placebo (N = 634)
Mean trial follow-up — days	27.4	27.5
Mean time at risk for event — days	13.1	13.7
No. of participants with sustained alleviation (%)	477 (72.9)	470 (74.1)
Time to sustained alleviation		
Median (95% CI) — days	12 (11–13)	13 (12–14)
Mean — days	13.8	14.1
P value by log-rank test	0.60	

# VV116 vs. PAXLOVID in high-risk patients

## Time to sustained clinical recovery and symptom resolution

**Table 2.** Primary and Secondary Efficacy End Points (Full Analysis Population).<sup>\*,‡</sup>

End Point	VV116 (N = 384)	Nirmatrelvir–Ritonavir (N = 387)
<b>Primary end point<sup>†</sup></b>		
25th percentile of time to sustained clinical recovery (95% CI) — days	4.0 (3.0–4.0)	4.0 (3.0–4.0)
Median time to sustained clinical recovery — days	4.0	5.0
Hazard ratio vs. nirmatrelvir–ritonavir (95% CI) <sup>‡</sup>	1.17 (1.02–1.36)	—
<b>Secondary end points</b>		
Progression to severe Covid-19 or death by day 28 — no. (%)	0	0
Median time to sustained symptom resolution (95% CI) — days <sup>§</sup>	7.0 (7.0–8.0)	7.0 (7.0–8.0)
Hazard ratio vs. vs. nirmatrelvir–ritonavir (95% CI) <sup>‡</sup>	1.06 (0.91–1.22)	—

The primary end point was assessed in the primary analysis (data-cutoff date, May 13, 2022), and the data were updated in the final analysis (data-cutoff date, August 18, 2022). The updated data are reported here. Participants were those who underwent randomization and received at least one dose of VV116 or nirmatrelvir–ritonavir. Participants were grouped according to treatment assignment. CI denotes confidence interval

*\* The trial was limited to patients infected with omicron variant*

Source: Cao et al, NEJM, Feb 2, 2023

# XOFLUZA pivotal trials in uncomplicated Influenza

## Time to symptom alleviation through day 28

**Table 5 Time to Alleviation of Symptoms after Single Dose in Adult Subjects with Acute Uncomplicated Influenza in Trial 1 (Median Hours)**

	<b>XOFLUZA 40 mg (95% CI<sup>1</sup>) N = 100</b>	<b>Placebo (95% CI<sup>1</sup>) N = 100</b>
<b>Adults (20 to 64 Years of Age)</b>	50 hours <sup>2</sup> (45, 64)	78 hours (68, 89)

<sup>1</sup>CI: Confidence interval

<sup>2</sup>XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Gehan-Breslow's generalized Wilcoxon test (p-value: 0.014, adjusted for multiplicity). The primary analysis using the Cox Proportional Hazards Model did not reach statistical significance (p-value: 0.165).

**Table 6 Time to Alleviation of Symptoms after Single Dose in Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 2 (Median Hours)**

	<b>XOFLUZA 40 mg or 80 mg<sup>1</sup> (95% CI<sup>2</sup>) N = 455</b>	<b>Placebo (95% CI<sup>2</sup>) N = 230</b>
<b>Subjects (≥ 12 Years of Age)</b>	54 hours <sup>3</sup> (50, 59)	80 hours (73, 87)

<sup>1</sup>Dosing was based on weight. Subjects weighing < 80 kg received a single 40 mg dose and subjects ≥ 80 kg received a single 80 mg dose.

<sup>2</sup>CI: Confidence interval

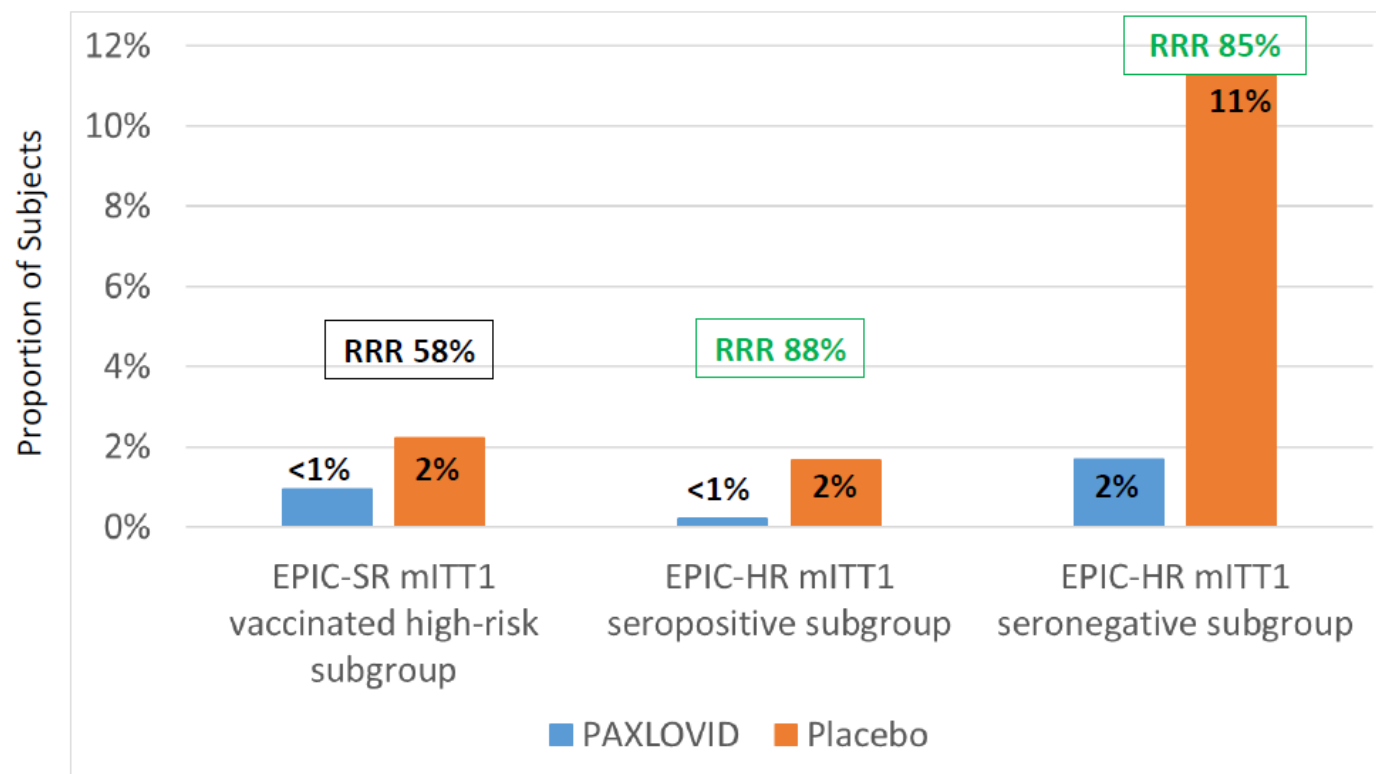
<sup>3</sup>XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Peto-Prentice's generalized Wilcoxon test (p-value: <0.001).

Source: Xofluza, FDA Label

# Impact of vaccination and seropositivity

## PAXLOVID Efficacy in high-risk patients

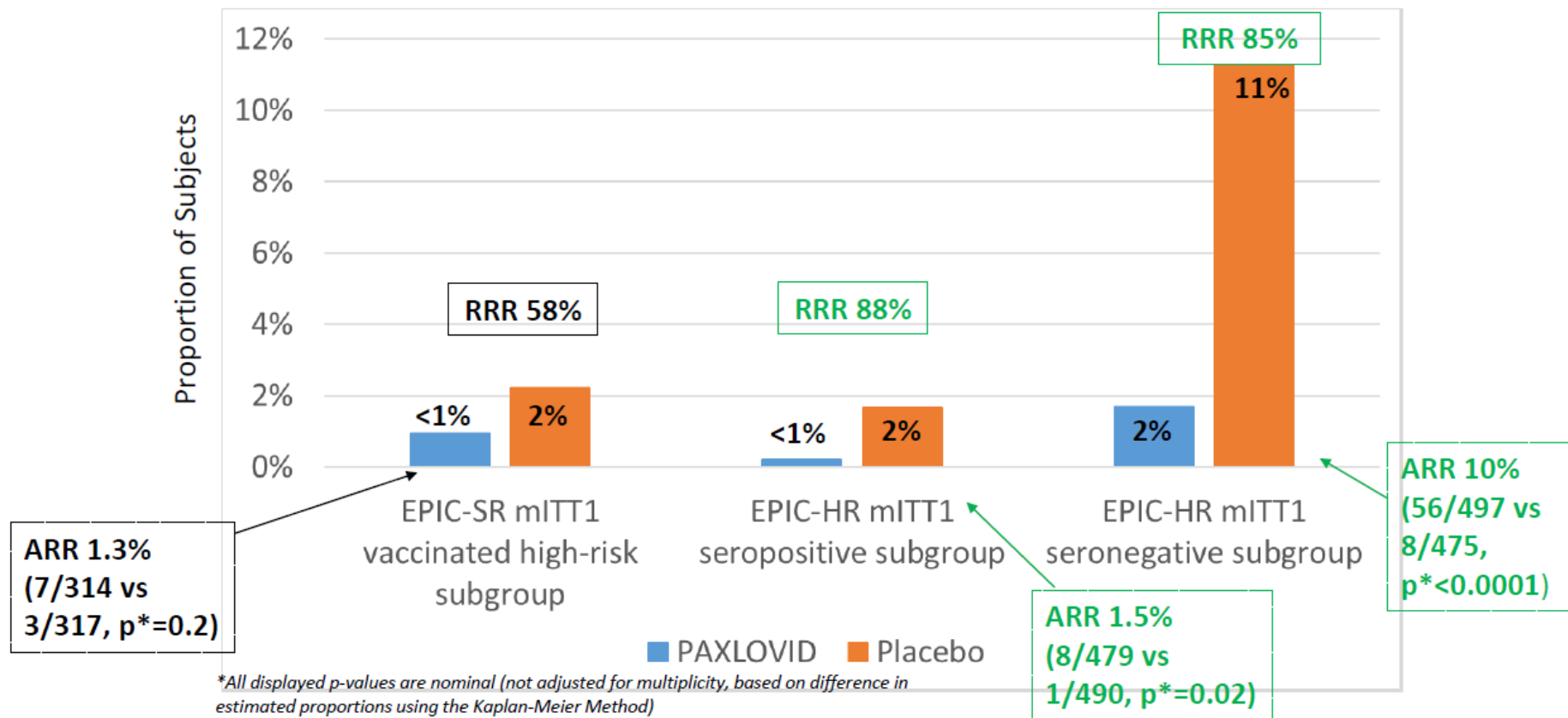
### COVID-19-Related Hospitalization or Death From Any Cause Through Day 28



# Impact of vaccination and seropositivity

## PAXLOVID Efficacy in high-risk patients

### COVID-19-Related Hospitalization or Death From Any Cause Through Day 28

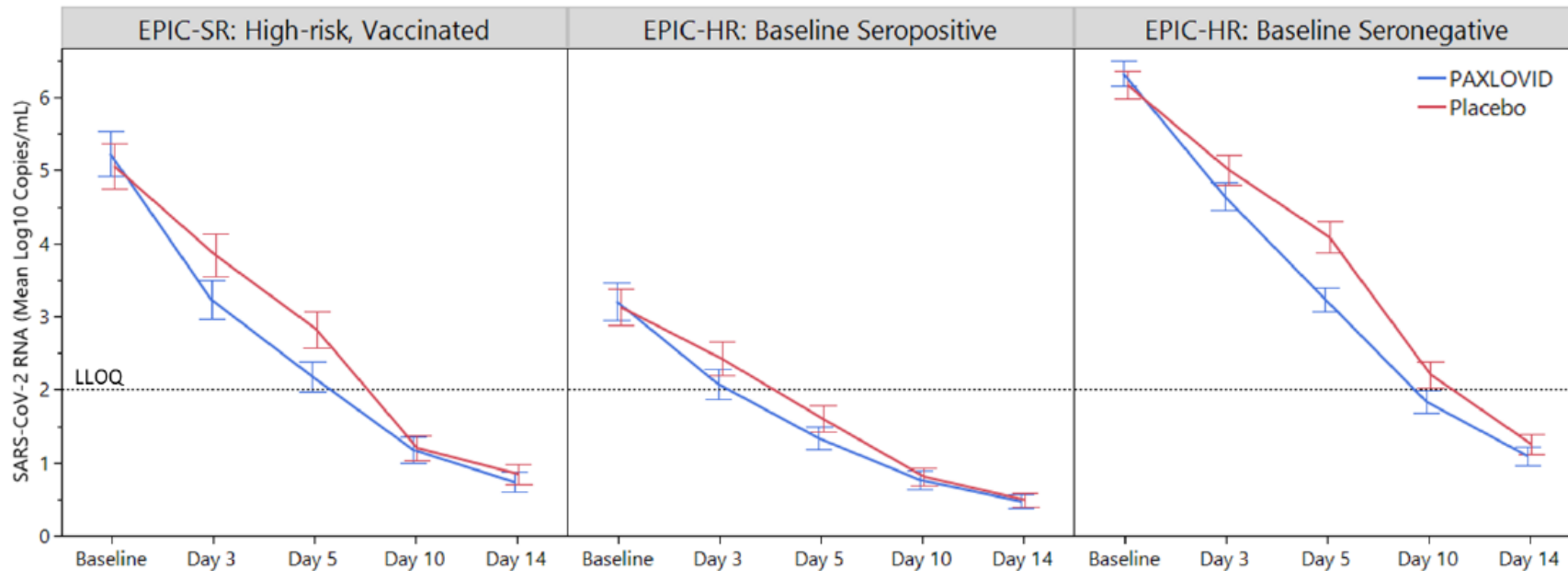


# Impact of vaccination and seropositivity

## PAXLOVID antiviral efficacy



### SARS-CoV-2 RNA Levels Over Time

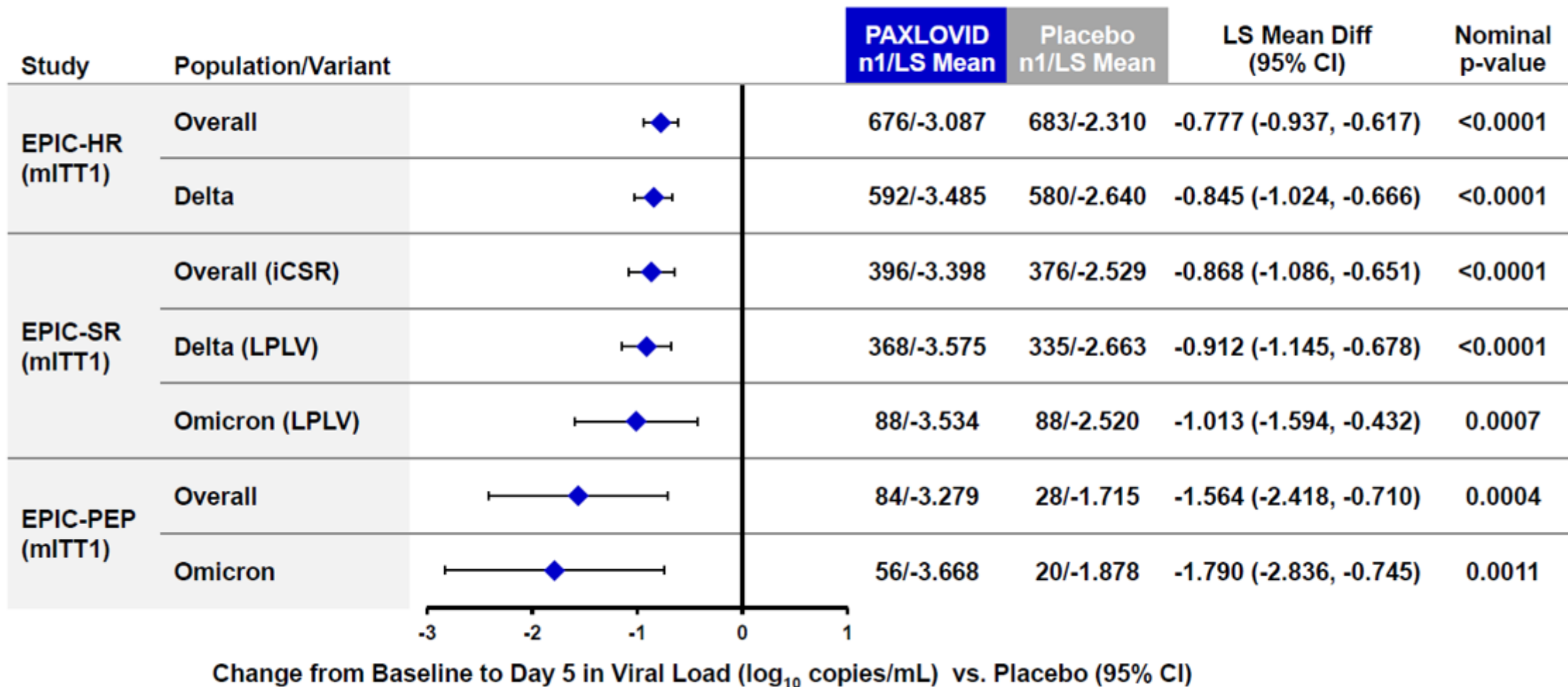


Abbreviations: LLOQ, lower limit of quantification

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.

# Analysis of Change from Baseline to Day 5 in Viral Load by Variant

## EPIC-HR, EPIC-SR, and EPIC-PEP



C4671002 iCSR Overall (mITT1): interim snapshot Dec 2021; C4671002 Delta/Omicron: LPLV datacut; C4671005 and C4671006: LPLV datacut  
 CI=Confidence Interval, LS=Least Squares, mITT1=modified intent-to-treat 1

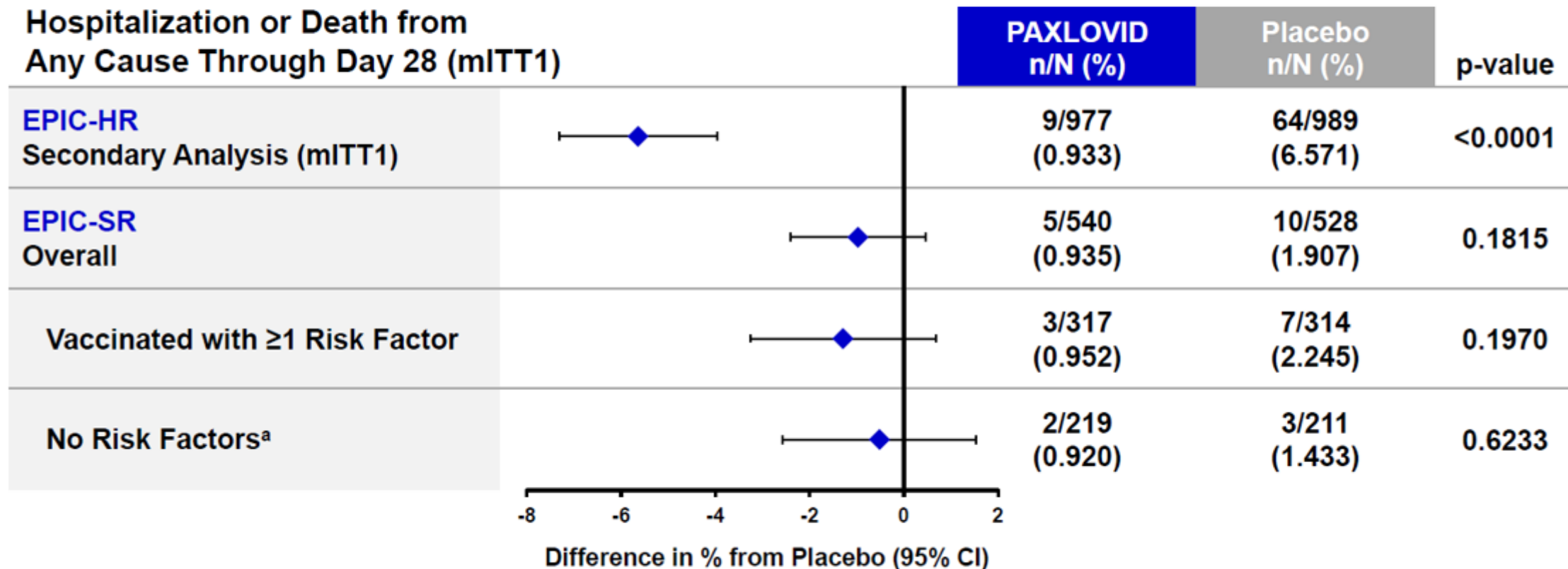
Source: FDA AdCom Meeting for Paxlovid, March 16, 2023

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# Reduction in Risk of COVID-19 Related Hospitalization or Death Regardless of Vaccination Status

EPIC-HR and EPIC-SR

Hospitalization or Death from  
Any Cause Through Day 28 (mITT1)



a. Includes participants who were or were not vaccinated  
Kaplan-Meier Method; difference of the estimated proportions, 95% CI and p-value based upon normal approximation.  
mITT1=modified intent-to-treat 1

Source: FDA AdCom Meeting for  
Paxlovid, March 16, 2023<sup>16</sup>

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# A few questions for deliberation...

- Viral load
  - Should viral load reduction be used as a co-primary endpoint or be included as one of the components of a composite primary endpoint?
- Time to sustained alleviation or resolution of symptoms
  - What is the clinically meaningful treatment effect size?
  - Which symptoms are more clinically meaningful ?
- Covid related emergency room or medical visits
  - Can these be incorporated in the composite primary endpoint as a surrogate for disease progression?

**Thank you!**