PAXLOVID (nirmatrelvir / ritonavir)

Main Protease Inhibitor of SARS-CoV-2 Corona Virus

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Chief Development Officer,
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Global Product Development, Pfizer Inc.

Antimicrobial Drugs
Advisory Committee

16 March 2023

Agenda

Subject	Presenter
Introduction	**James Rusnak, MD, PhD** *Senior Vice President; Chief Development Officer,* *Internal Medicine, Anti-infectives, and Hospital* *Global Product Development, Pfizer Inc.*
Efficacy from EPIC Randomized Clinical Trials	**Jennifer Hammond, PhD** *Vice President* *Development Head Antivirals* *Global Product Development, Pfizer Inc.*
Effectiveness from Real-World Studies	**John McLaughlin, PhD** *Vice President, Global Medical Lead COVID and Influenza* *Pfizer, Inc.*
Efficacy Conclusions and Safety from EPIC Randomized Clinical Trials	**Jennifer Hammond, PhD**
Safety from Post-Marketing Surveillance	**Lubna Merchant, MS, PharmD** *Director, Risk Management Center of Excellence,* *Worldwide Safety, Pfizer Inc.*
COVID-19 Rebound, Continued Development, and Conclusions	**James Rusnak, MD, PhD**

PAXLOVID

An Oral Antiviral Containing Nirmatrelvir and Ritonavir, Co-Packaged

Emergency Use Authorization issued 22 December 2021

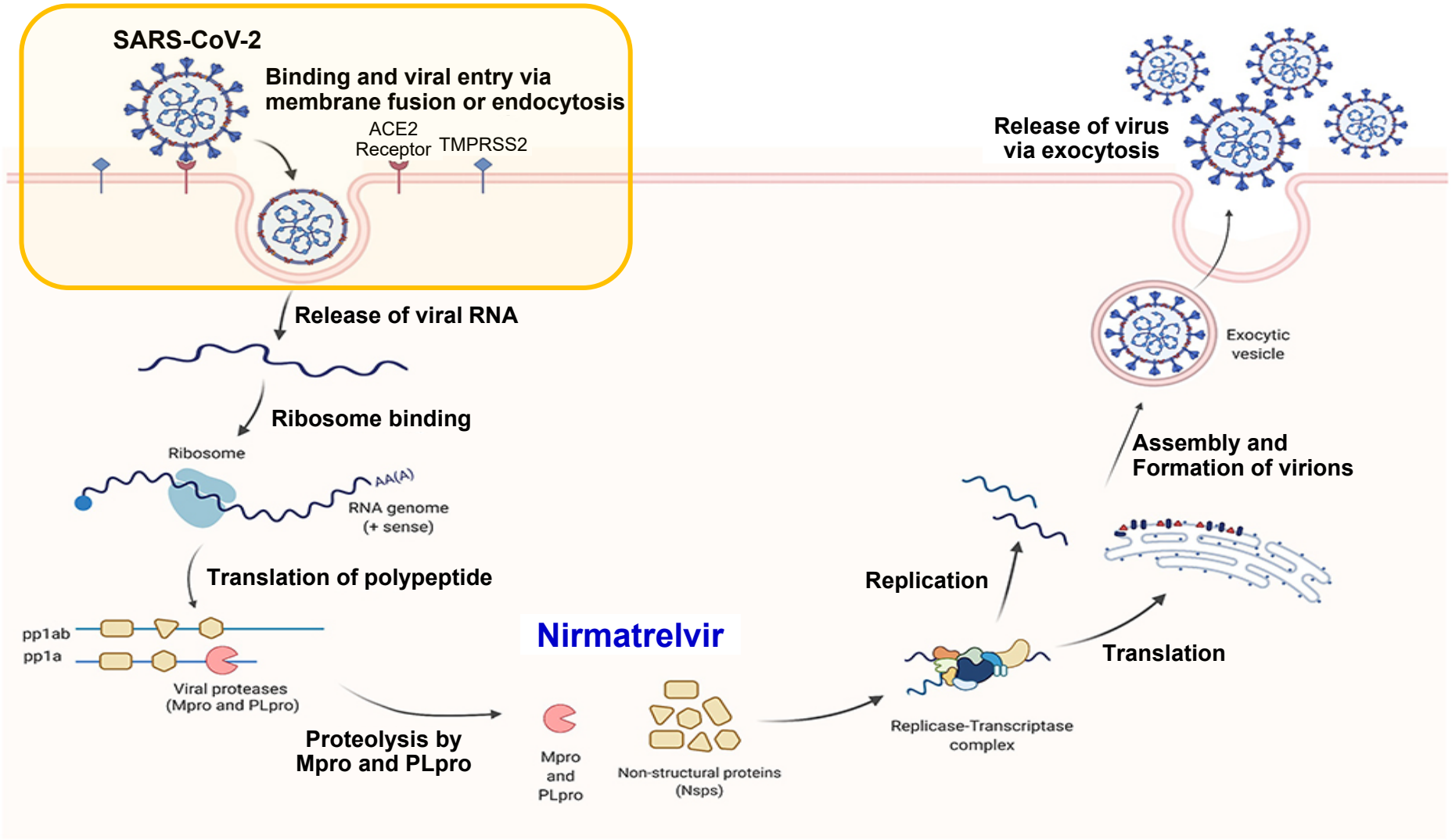
Orally administered together twice daily for 5 days

- Nirmatrelvir 300 mg (two 150 mg tablets): inhibitor of the SARS-CoV-2 Virus Main Protease
- Ritonavir 100 mg (one 100 mg tablet): not pharmacologically active against SARS-CoV-2, co-administered to enhance nirmatrelvir pharmacokinetics
- Reduced dose for impaired renal function eGFR <60 mL/min, no dose adjustment in mild-moderate hepatic impairment

PROPOSED INDICATION

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.

SARS-CoV-2 Main Protease: Essential to Viral Replication



Alzyoud, L., M. A. Ghattas and N. Atatreh (Drug Design, Development and Therapy. Aug 2022 Volume 16, pp 2463-2478)

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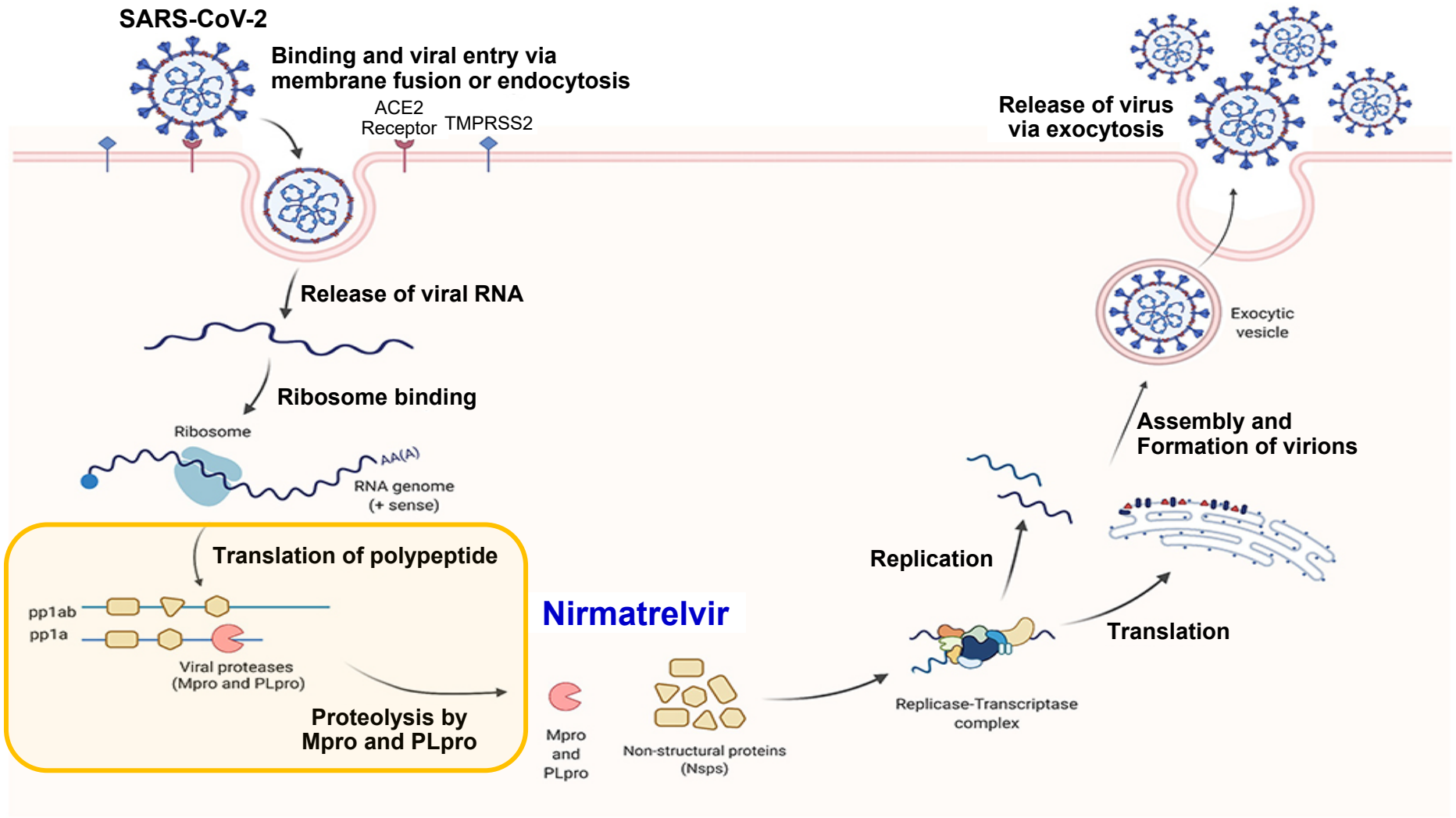

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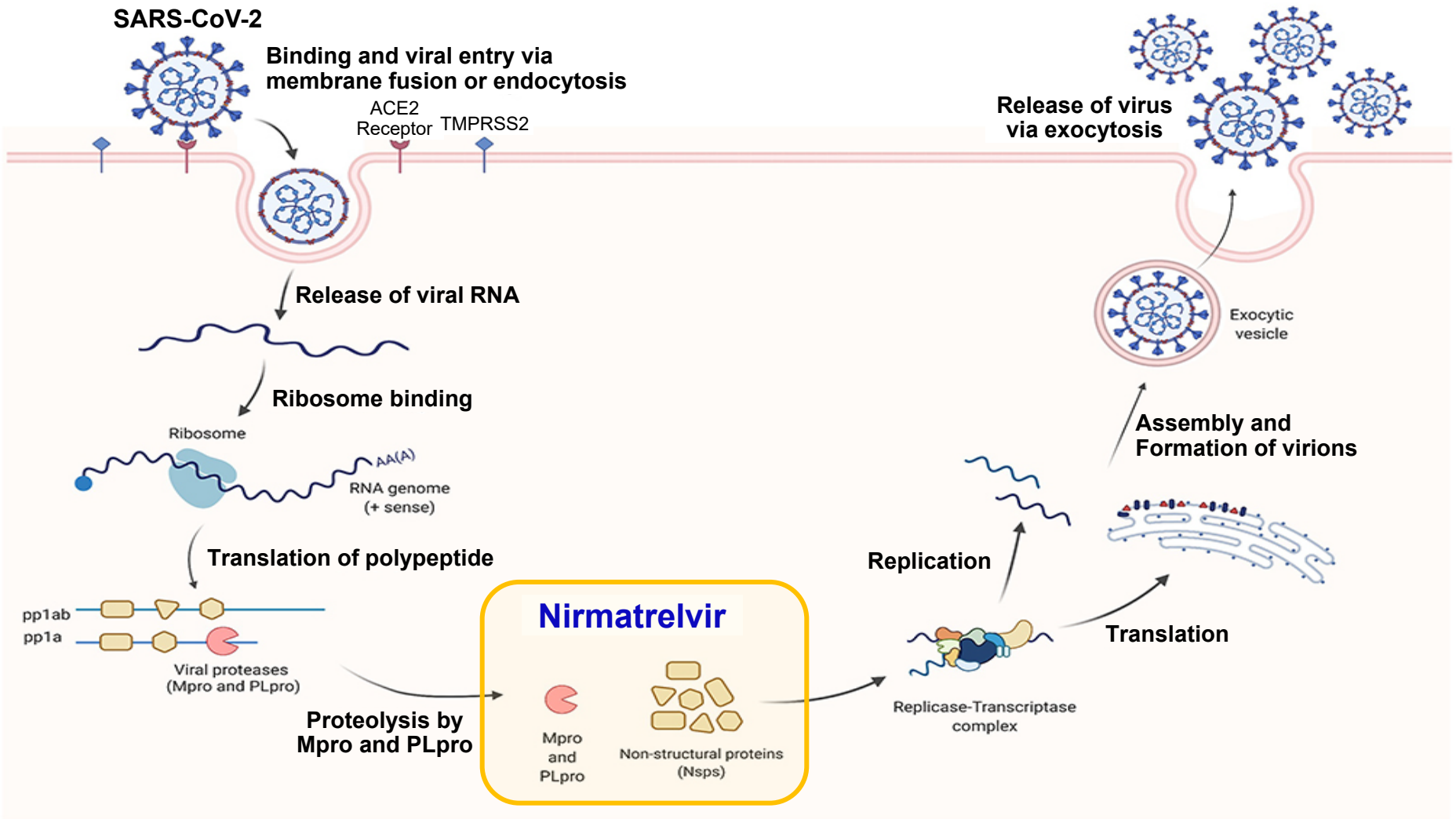

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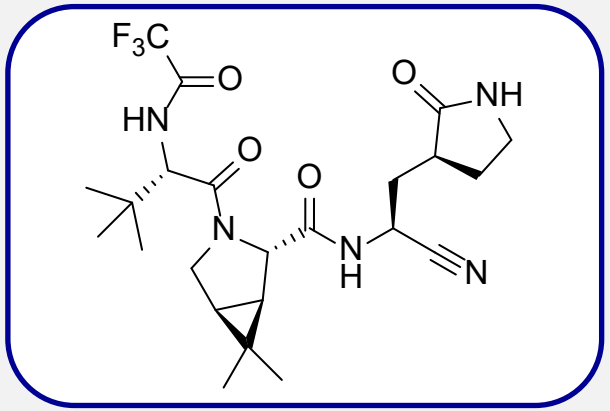
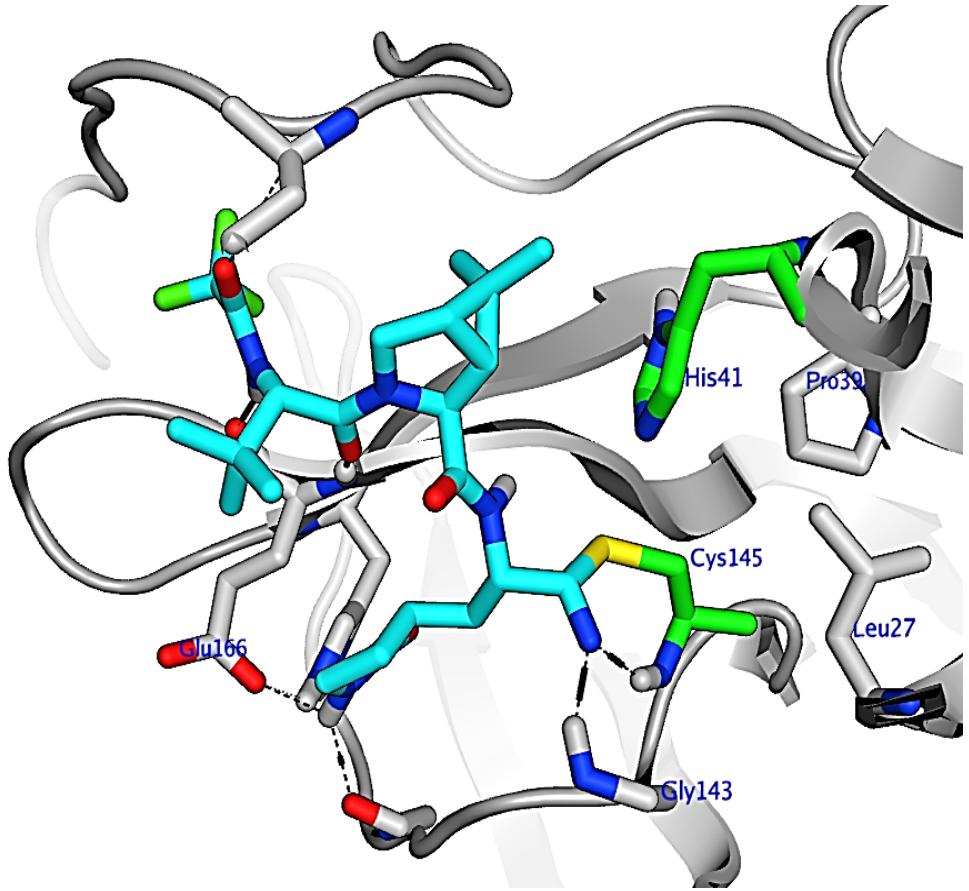
Nirmatrelvir is a Potent and Selective SARS-CoV-2 M^{pro} Inhibitor with Robust Pre-clinical Safety Profile



- Nirmatrelvir binds to the M^{pro} active site forming a reversible covalent adduct with the catalytic cysteine, Cys145: K_i = 3 nM
- Through M^{pro} inhibition nirmatrelvir prevents viral replication: Antiviral activity in human airway epithelial cells; EC_{50} = 61.8 nM, EC_{90} = 181 nM[1]
- Nirmatrelvir has good selectivity over human targets and no adverse findings in 1 month rat and monkey toxicity studies, no genetic toxicity



1. Owen et al Science 2021; Satish et al, *Int. J. Toxicol* 2022

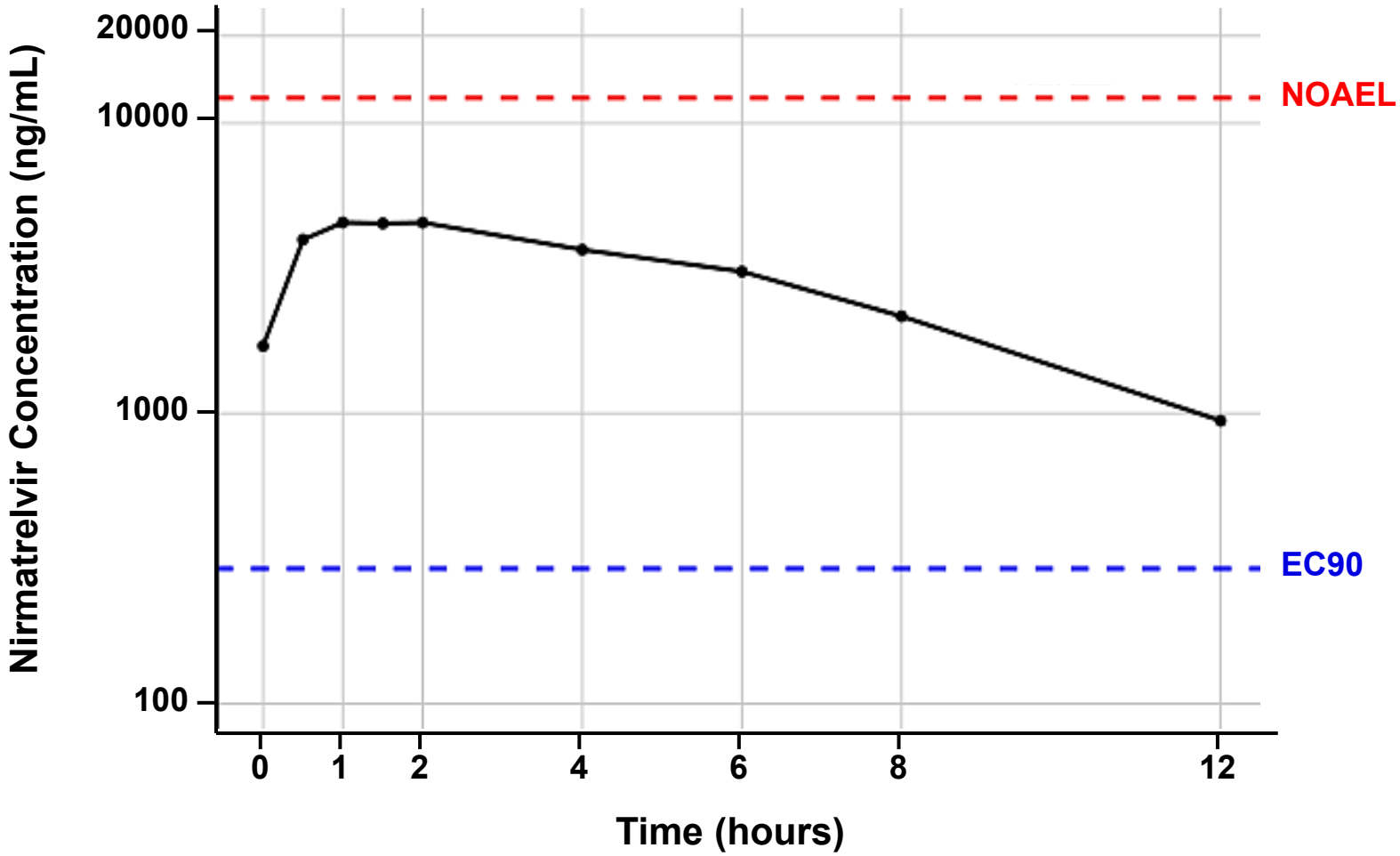
Nirmatrelvir Retains Consistent, Potent in-vitro Anti-viral (AV) Activity Across SARS-CoV-2 Variants

Variant	M^{pro} Mutations	Variant Fold EC_{50} Relative to WT EC_{50} (n≥3)[a]
Washington	Wildtype	--
Alpha	N/A (same as WT)	~1
Beta B.1.351	K90R (99%)	~4
Delta	N/A (same as WT)	~0.5
Gamma	N/A (same as WT)	~1
Lambda	G15S (93%)	~0.6
Omicron BA.1	P132H (100%)	~0.5
Omicron variants: BA.2	P132H (100%)	~1
BA.2.12.1	P132H (100%)	~0.6
BA.4	P132H (100%)	~0.6
BA.5	P132H (100%)	~0.6
BF.7[b]	P132H (100%), P252L (31%), F294L (70%)	~1
BF.7[b]	P132H (100%), T243I (100%)	~0.8
BQ.1.11[b]	P132H (100%)	~0.9[c]
BQ.1[b]	P132H (100%)	~1
XBB.1.5[b]	P132H (100%)	~1

a. Cell type – Vero E6 P-gp KO or Vero E6 TMPRSS2; b. New data as of Feb. 27, 2023; c. n=2
Source: Pfizer Internal Data, Report #042713

PAXLOVID (nirmatrelvir/ritonavir) Maintains Plasma Concentrations at Multiples Above the AV Cellular EC_{90} Throughout the Dosing Period

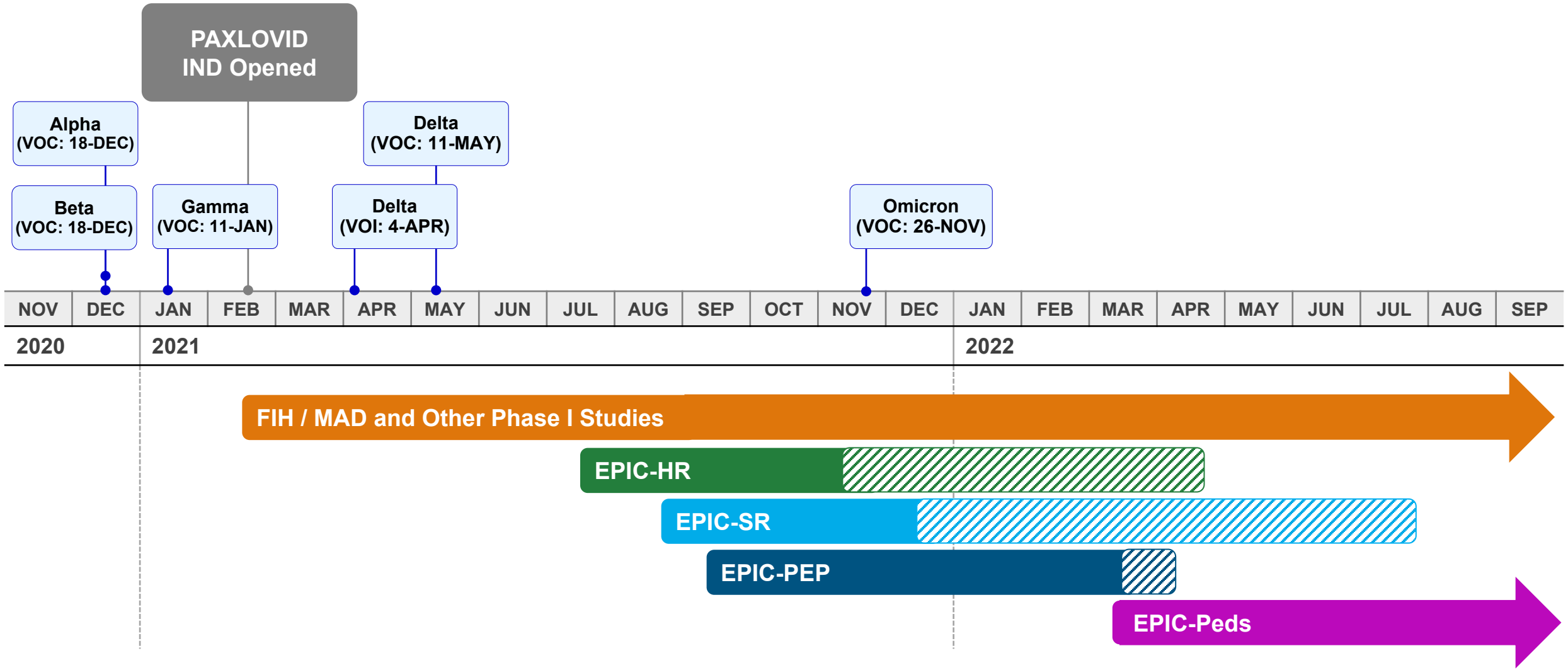
Mean Steady-State Plasma Nirmatrelvir Concentrations[a]



a. Healthy Volunteer Study C4671015

Large Clinical Development Program

Safety and Efficacy Evaluated in >6000 Participants in 21 Countries



WHO, Oct 2021 Variants of Interest / Variants of Concern

Severe Illness from COVID-19 Remains a Serious Public Health Threat

- **COVID-19 continues to cause significant burden in the US**
  - ~ 200,000 reported cases each week[1]
    - For each reported case, an estimated 7-10 cases are unreported[2]
  - 3000-4000 hospital admissions daily[1]
  - 300-400 deaths daily[1]
- **≥176M US adults are at increased risk of severe COVID-19[3]**
  - Almost 9 out of every 10 COVID-19 deaths are among older adults aged ≥65 years[4]
- **COVID-19 can cause long-term sequelae (or long COVID). Severe COVID-19 illness is associated with increased risk of long COVID[5]**
- **SARS-CoV-2 is unpredictable. Treatment options are needed to address the significant burden and uncertainty of COVID-19**

1. Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, February 23. https://covid.cdc.gov/covid-data-tracker; 2. CNN. (2022). Why the Omicron offshoot BA.5 is a big deal. (2022, July 18). Available from: https://www.cnn.com/2022/07/14/health/omicron-ba-5-variant-immunity-severity/. Accessed on: 23 Feb 2023.; 3. Ajufo et al. Am J Prev Cardiol 2021. doi: 10.1016/j.ajpc.2021.100156; 4. Centers for Disease Control and Prevention. Provisional Death Counts for Coronavirus Disease 2019 (COVID-19). Atlanta, GA: US Department of Health and Human Services, CDC; 2023, February 23. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm; 5. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, December 16. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

Presentation Objectives

- **To demonstrate that the benefit-risk balance of PAXLOVID is positive in the context of:**
  - Efficacy and safety profile
  - Intended patient population
  - Safety surveillance and risk management
- **To establish that the available data supports approval of the full marketing authorization of PAXLOVID for the treatment of COVID-19 in vaccinated or unvaccinated adult patients who have risk factors for severe COVID-19 illness**

Efficacy from EPIC Randomized Clinical Trials

Jennifer Hammond, PhD
Vice President
Development Head Antivirals
Global Product Development, Pfizer Inc.

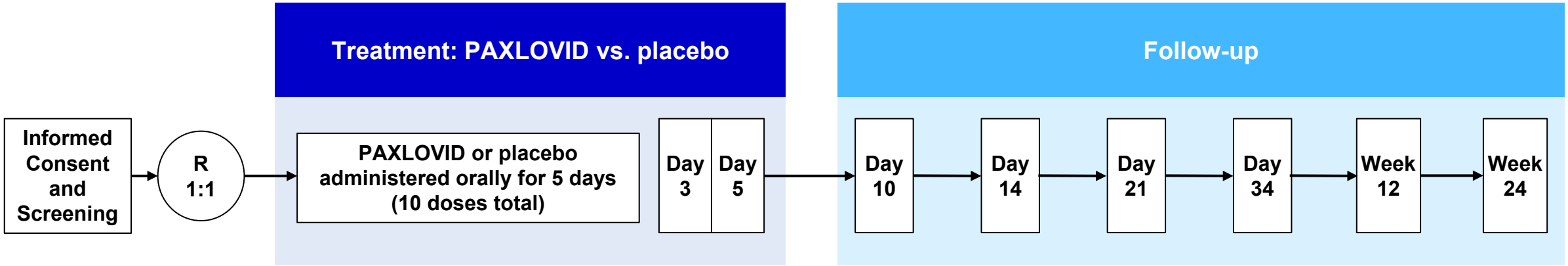
Efficacy Presentation

- **Pivotal Study C4671005 (EPIC-HR)**
  - Unvaccinated adult participants with ≥1 risk factor for severe COVID-19 illness
  - Primary endpoint - Proportion of participants with COVID-19 related hospitalization or all-cause death through Day 28
- **Supportive Studies**
  - C4671002 (EPIC-SR)
    - Participants at standard risk for severe COVID-19 illness (unvaccinated with no risk factors or fully vaccinated with at least 1 risk factor for severe COVID-19 illness)
  - C4671006 (EPIC-PEP)
    - Participants who were asymptomatic, tested negative for SARS-CoV-2 infection and were exposed to SARS-CoV-2 by a recently diagnosed household contact

Study Design

Pivotal Study C4671005 (EPIC-HR)

Phase 2/3 safety and efficacy study in unvaccinated, symptomatic adult participants with confirmed COVID-19 who have at least 1 risk factor[a] for developing severe COVID-19 illness



Screening / Baseline and Day 5 visits conducted in-person, all other visits conducted as in-person or telemedicine visits

Patient daily diary entry for COVID-19 signs and symptoms (Day 1 to 28)

Viral RNA (RT-PCR) assessments at Baseline, Days 3, 5, 10 and 14

Day 28 Primary Endpoint
Proportion of participants with COVID-19 related hospitalization or All-cause Death through Day 28

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

Demographics and Baseline Characteristics

Study C4671005 EPIC-HR, Full Analysis Set (N=2113)

Demographics	
Gender	**Female: 49.4% / Male: 50.6%**
Race	White = 70.8%; Black = 4.2%; Asian = 14.9%
Ethnicity	Hispanic or Latino = 41.3%

Age (years), n (%)			
Mean (SD)	**≥60**	**<75**	**≥75**
45.4 (15.5)	438 (20.7)	2049 (97.0)	64 (3.0)

Body Mass Index (kg/m^2), n (%)			
Mean (SD)	**≥25**	**<30**	**≥30**
29.1 (5.6)	1692 (80.1)	1357 (64.2)	755 (35.7)

Risk Factors for Severe COVID-19 Illness				
Number of Risk Factors[a]	**1**	**2**	**3**	**≥4**
	40.2%	35.7%	16.2%	7.9%

Comorbidities with Prevalence ≥1%, n (%)	
Cardiovascular	87 (4.1)
Chronic lung disease	100 (4.7)
Diabetes mellitus	228 (10.8)
Hypertension	671 (31.8)
Cigarette smoker	826 (39.1)

Baseline Characteristics of SARS-CoV-2 Infection					
Serology Status, n (%)	**Negative**			**Positive**	
	1034 (48.9)			1037 (49.1)	
Baseline Viral Load (log_{10} Copies / mL)	**0**	**<4**	**≥4**	**<7**	**≥7**
	16.6%	34.7%	61.9%	69.6%	26.9%
Days Since First Symptom, n (%)	**≤3**			**>3**	
	1418 (67.1)			695 (32.9)	

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94% of PAXLOVID Treated Participants Completed Treatment in EPIC-HR

	PAXLOVID N=1049 n (%)	Placebo N=1064 n (%)
Participants who entered treatment[a]	1049 (100)	1064 (100)
Completed treatment	**986 (94.0)**	**979 (92.0)**
Discontinued treatment for any reason	63 (6.0)	85 (8.0)
Withdrawal by subject	**30 (2.9)**	**27 (2.5)**
Adverse Event	21 (2.0)	45 (4.2)
Other	9 (0.9)	11 (1.0)
No longer meets eligibility criteria	3 (0.3)	1 (<0.1)
Medication error without associated AE	0	1 (<0.1)
Death	0	0
Lack of efficacy	0	0
Lost to follow-up	0	0
Pregnancy	0	0
Protocol deviation	0	0
Noncompliance with study drug	0	0

Full Analysis Set (FAS)

Clinically and Statistically Significant Benefits Across Multiple Endpoints

EPIC-HR

PAXLOVID administered twice daily results in:

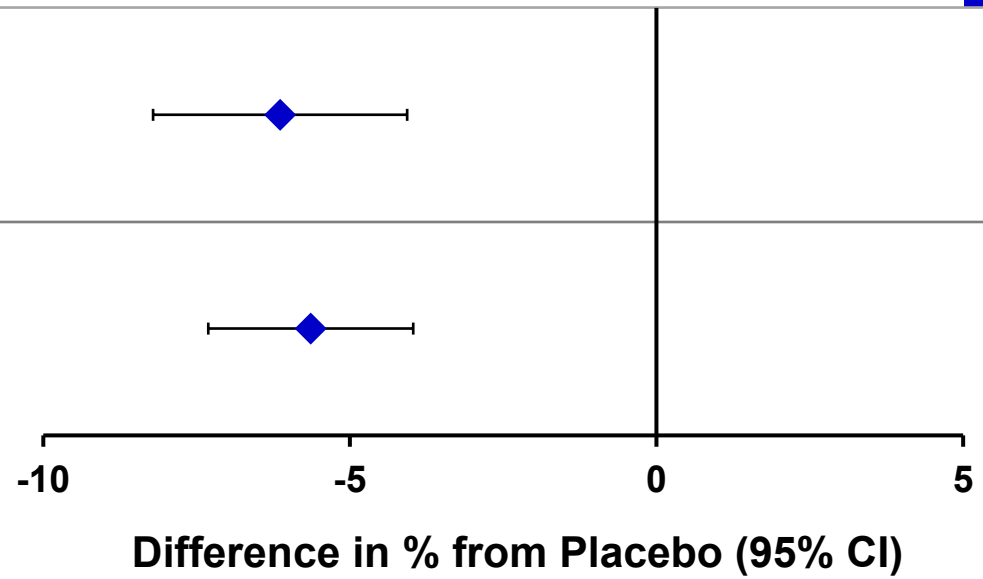
- **89.1% (-6.1% difference, p<0.0001) and 85.8% (-5.6% difference, p<0.0001) reduction in the proportion of participants with COVID-19 related hospitalization or all-cause death through Day 28 when treatment was initiated within 3 days (primary endpoint) or 5 days (key secondary endpoint) of symptom onset, respectively**
  - Consistent efficacy across prespecified subgroup analyses of primary endpoint by participant demographic and baseline characteristics
  - No deaths for PAXLOVID treated participants and 15 total deaths, 13 by Day 34 and 2 during long-term follow-up (post-Day 34) for placebo treated participants
- **PAXLOVID associated with 2- and 3-day reductions in median time to sustained alleviation and resolution of all targeted COVID-related symptoms, respectively and PAXLOVID treated participants were 27% (p<0.0001) and 20% (p=0.0022) more likely to achieve sustained alleviation and resolution compared with placebo**
- **73% relative risk reduction compared to placebo in COVID-19 related medical visits**
- **Placebo-adjusted reduction of 0.78 $\log_{10}$ copies/mL (p<0.0001) in SARS-CoV-2 viral RNA concentration at 5 days after initiation of treatment**

mL=milliliter

Significant Reduction in COVID-19 Related Hospitalization or All-cause Death when Treatment is Initiated within 3 or 5 Days of Symptom Onset

EPIC-HR

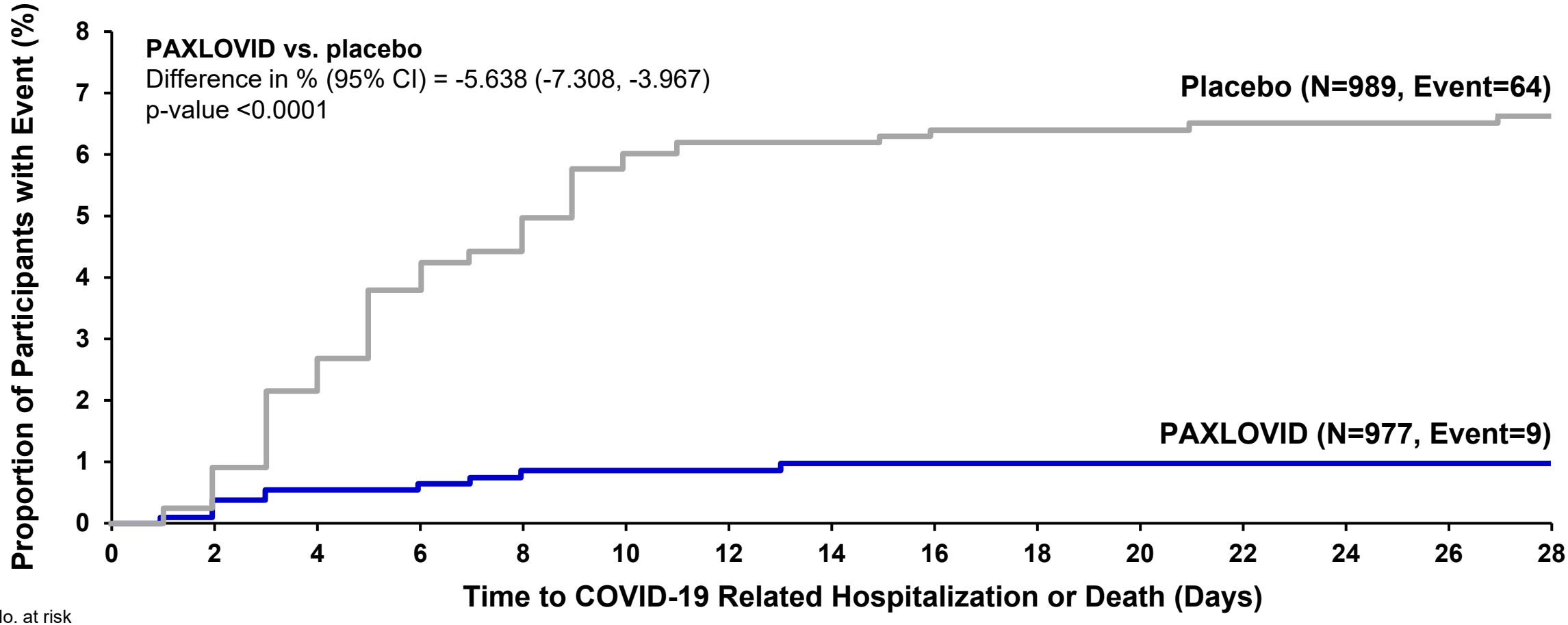
	PAXLOVID n/N (%)	Placebo n/N (%)	p-value
Primary Analysis (mITT)	5/671 (0.752)	44/647 (6.888)	<0.0001
Secondary Analysis (mITT1)	9/977 (0.933)	64/989 (6.571)	<0.0001



Kaplan-Meier Method; difference of the estimated proportions, 95% CI and p-value based upon normal approximation
mITT=modified intent-to treat, mITT1=modified intent-to-treat 1

Between Group Differences in Events of COVID-19 Hospitalization and All-cause Death Evident Beginning at Day 3

EPIC-HR, mITT1



No. at risk

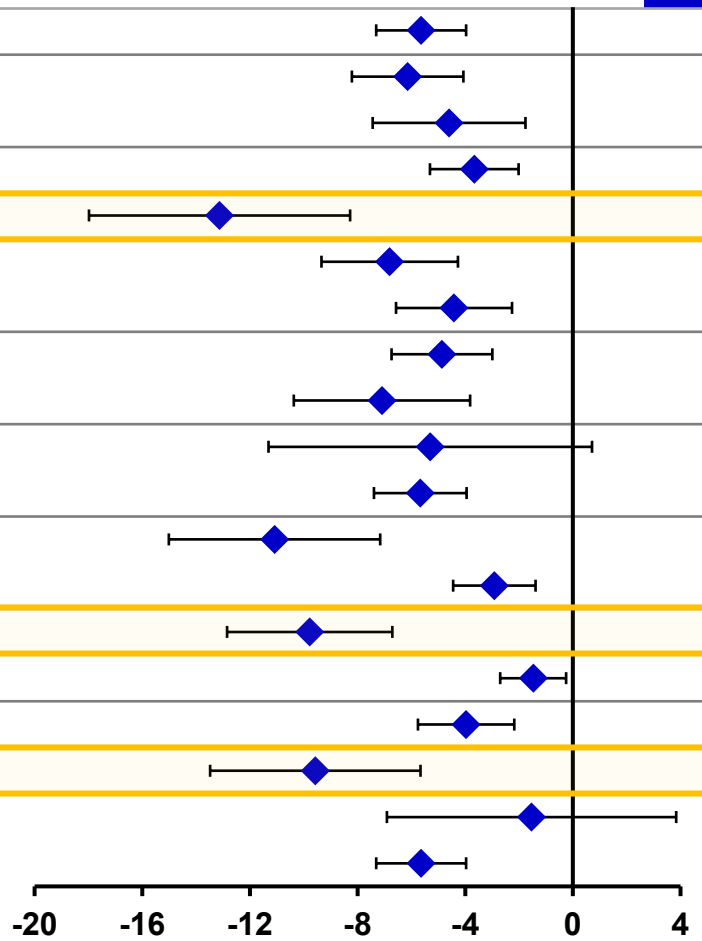
PAXLOVID	977	977	972	966	960	952	952	949	946	943	943	942	941	941	940	939	937	937	936	935	933	933	932	932	932	932	932	932	932
Placebo	989	989	985	975	959	947	935	929	922	917	908	906	904	904	904	902	900	899	898	897	896	896	893	893	893	893	893	893	892

Kaplan-Meier Method; difference of the proportions, 95% CI and p-value based upon normal approximation
mITT1=modified intent-to-treat 1

Consistent Reduction in Risk of COVID-19 Hospitalization or All-cause Death Across Prespecified Participant Subgroups

EPIC-HR, mITT1

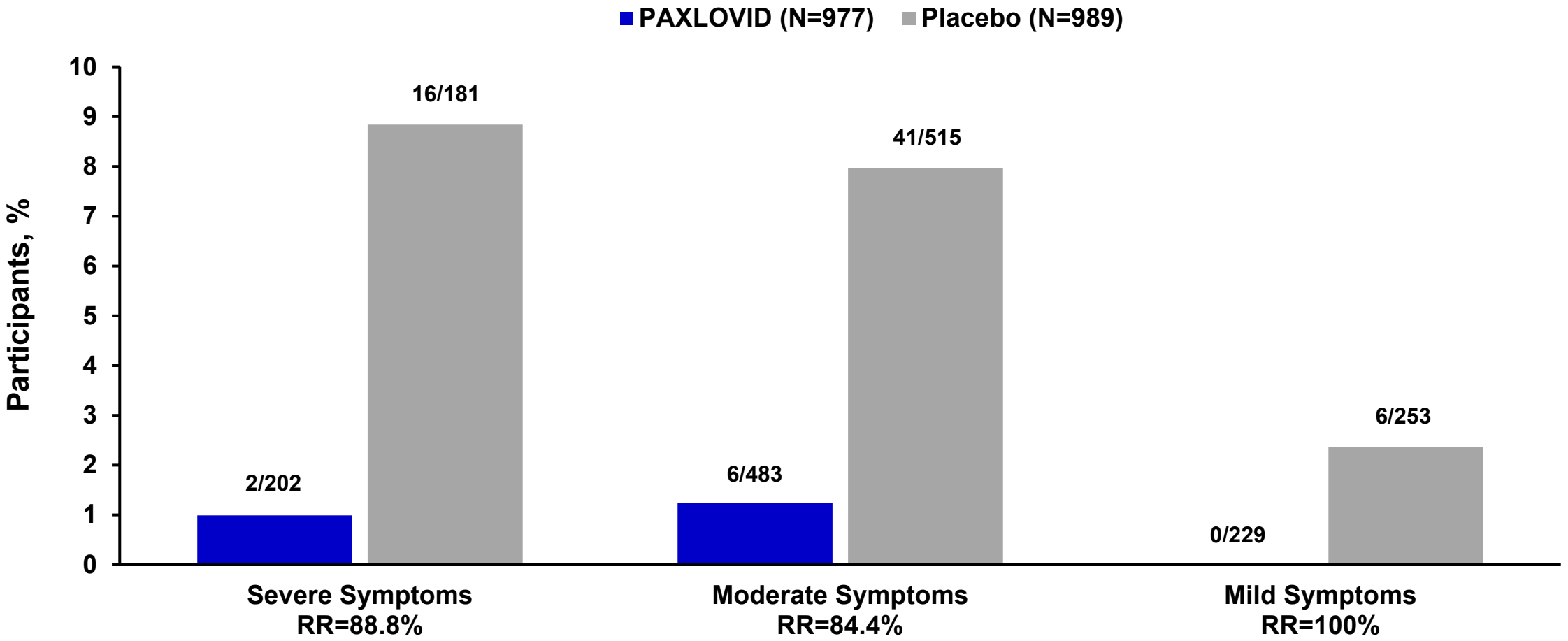
Category		PAXLOVID n/N	Placebo n/N	Relative Risk Reduction %
Overall		9/977	64/989	85.80
Symptom onset duration	≤3 days	5/671	44/647	89.09
	>3 days	4/306	20/342	77.51
Age	≤60 years	8/804	36/783	78.40
	>60 years	1/173	28/206	95.78
Gender	Male	5/485	39/505	86.68
	Female	4/492	25/484	84.30
BMI	<30 kg/m^2	4/641	35/644	88.57
	≥30 kg/m^2	5/336	29/345	82.41
Diabetes mellitus	Yes	3/106	9/111	65.05
	No	6/870	55/878	89.01
Hypertension	Yes	5/305	41/326	86.89
	No	4/671	23/663	82.88
Baseline SARS-CoV-2 serology status	Negative	8/475	56/497	85.09
	Positive	1/490	8/479	87.85
Viral load	<7	7/676	35/706	79.20
	≥7	2/273	26/256	92.64
Received/expected to receive COVID-19 mAbs tx[a]	Yes	1/61	2/64	48.36
	No	9/977	64/989	85.80



[a]mITT2 population
BL=Baseline, mITT1=modified intent-to-treat 1

Consistent Reduction in Risk of COVID-19 Hospitalization or Death Regardless of Baseline Symptom Severity

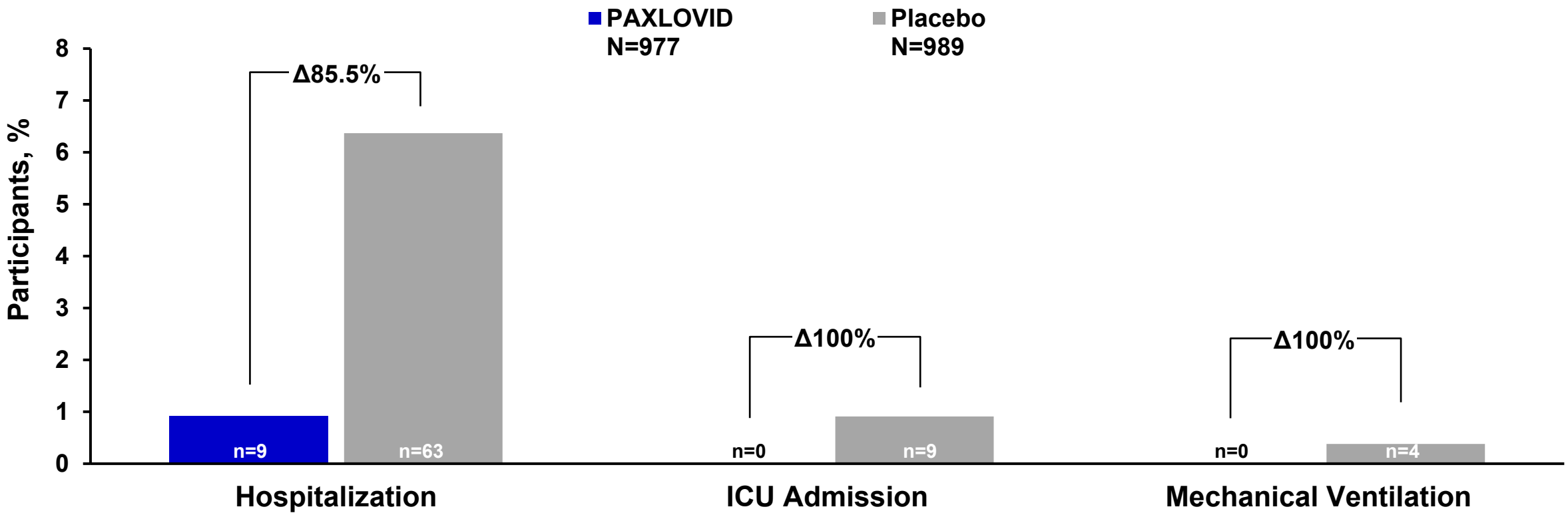
EPIC-HR, mITT1



mITT1=modified intent-to-treat 1; RR=risk reduction

Reduction in Risk of COVID-19 Hospitalization[a]

EPIC-HR, mITT1

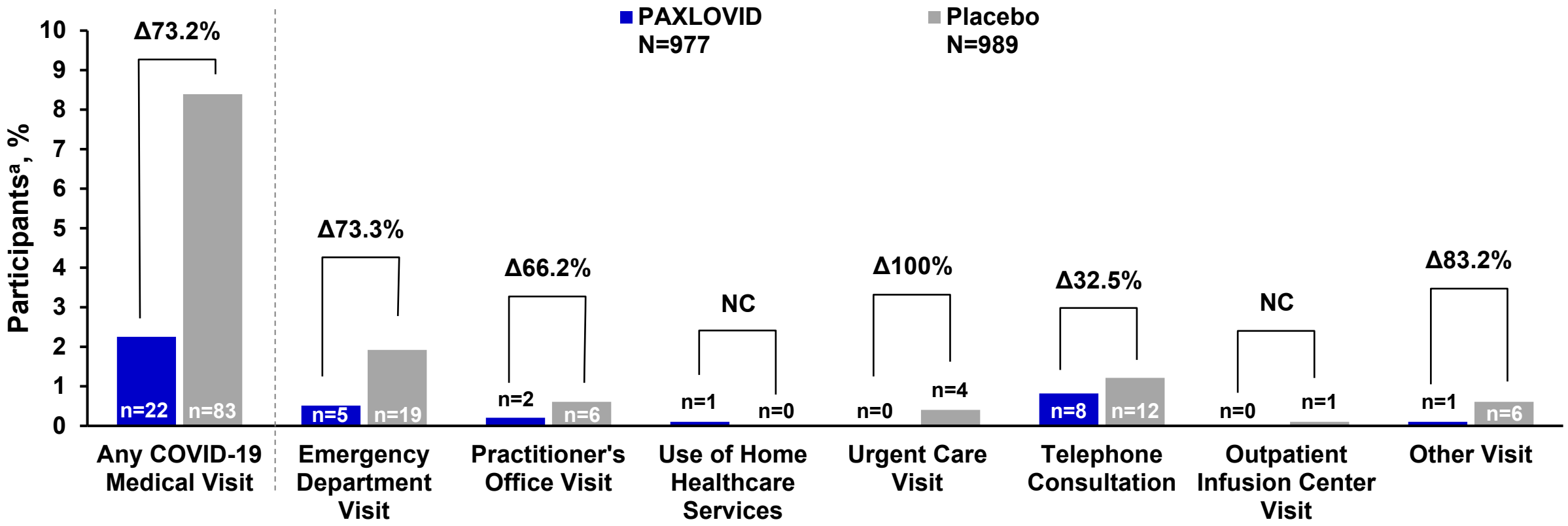


Among hospitalized participants with known discharge status, 100% of those who received PAXLOVID were discharged to home self care versus 54.7% of those receiving placebo

a. Not limited through Day 28.
Δ = percent reduction with PAXLOVID compared with placebo.
FAS=Full Analysis Set, ICU=intensive care unit, mITT1=modified intent-to-treat 1

Reduction in COVID-19 Health Care Utilization

EPIC-HR, mITT1[a]

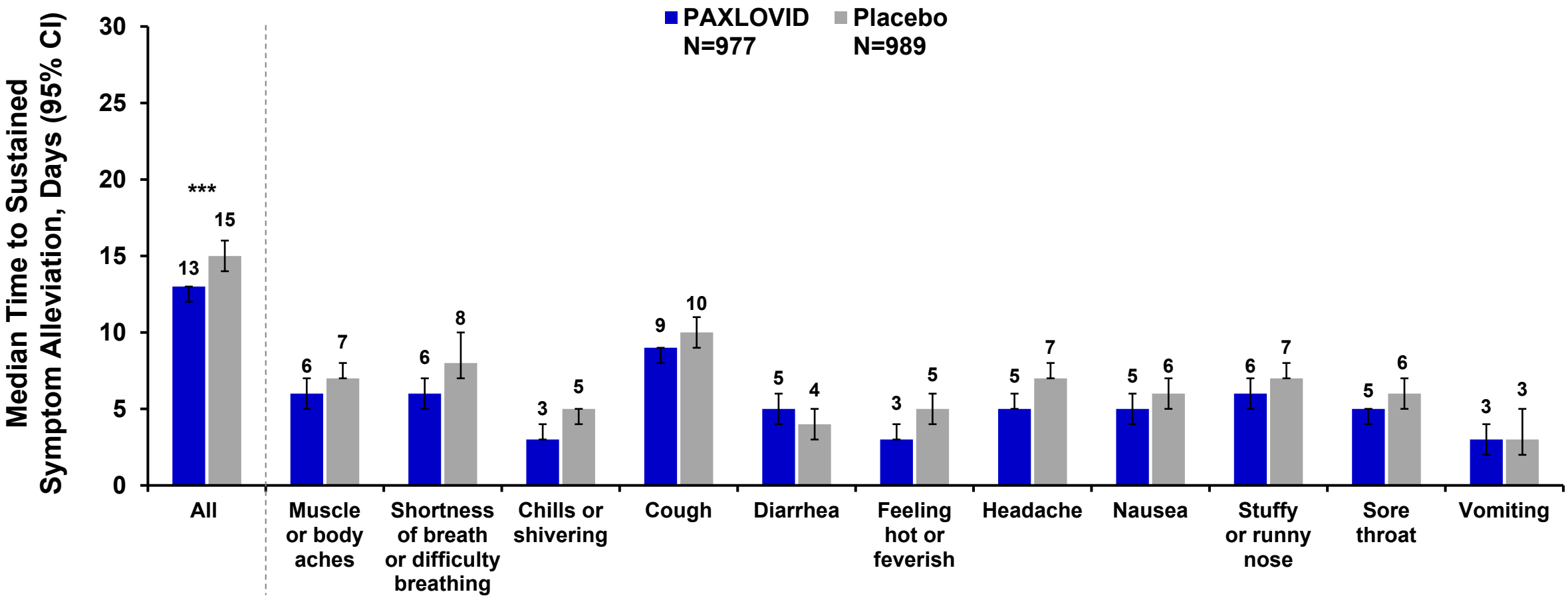


2.3% (22/977) with PAXLOVID and 8.4% (83/989) of participants who received placebo reported any COVID-19-related medical visit, corresponding to a 73% relative risk reduction with treatment

a. Not limited through Day 28.
Δ = percent reduction with nirmatrelvir / ritonavir compared with placebo.
mITT1=modified intent-to-treat 1, NC=not calculated

Reduction in the Time to Sustained Alleviation of Targeted COVID-19 Signs or Symptoms Through Day 28

EPIC-HR, mITT1



2 Day reduction (13 vs 15 days) in median time to sustained alleviation of all COVID-19 signs and symptoms and PAXLOVID treated participants were 27% (p<0.0001) more likely to achieve sustained alleviation compared with placebo

*p≤0.05; **p≤0.001; ***p≤0.0001 vs placebo
CI=Confidence Interval, mITT1=modified intent-to-treat 1

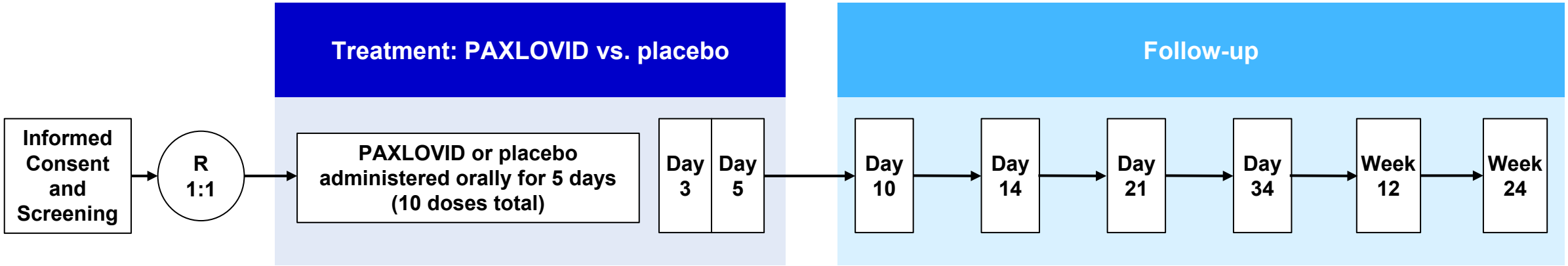
Efficacy Presentation

- **Pivotal Study C4671005 (EPIC-HR)**
  - Unvaccinated adult participants with ≥1 risk factor for severe COVID-19 illness
  - PAXLOVID twice daily x 5 days versus placebo
  - Proportion of participants with COVID-19 related hospitalization or all-cause death
- **Supportive Studies**
  - C4671002 (EPIC-SR)
    - Participants at standard risk for severe COVID-19 illness
      - Unvaccinated with no risk factors or fully vaccinated with risk factors for severe COVID-19 illness
    - PAXLOVID twice daily x 5 days versus placebo
    - Time to sustained alleviation of all targeted COVID-19 signs / symptoms
  - C4671006 (EPIC-PEP)
    - Participants who were asymptomatic, tested negative for SARS-CoV-2 infection and were exposed to SARS-CoV-2 by a recently diagnosed household contact
    - PAXLOVID twice daily x 5 days or 10 days versus placebo
    - Proportion of participants who developed symptomatic, RT-PCR or RAT confirmed SARS-CoV-2 infection

Study Design

Supportive Study C4671002 EPIC-SR

Phase 2/3 safety and efficacy study in symptomatic adult participants with confirmed COVID-19 who were considered to be at standard risk for severe COVID-19 illness unvaccinated and with no risk factors[a] or vaccinated with at least 1 risk factor for developing severe COVID-19 illness



Screening / Baseline and Day 5 visits conducted in-person, all other visits conducted as in-person or telemedicine visits

Patient daily diary entry for COVID-19 signs and symptoms (Day 1 to 28)

Viral RNA (RT-PCR) assessments at Baseline, Days 3, 5, 10 and 14

Day 28 Primary Endpoint
Time to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28

a. Risk Factors Include: Age ≥60, BMI >25 and Verbatim from pre-specified Medical History (Cigarette Smoker, Chronic Kidney Disease, Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence)

Demographics and Baseline Characteristics

Study C4671002 EPIC-SR mITT1 (N=1068)

Demographics	
Gender	Female: 52.3% / Male: 47.7%
Race	White = 78.5%; Black = 3.5%; Asian = 12.8%
Ethnicity	Hispanic or Latino = 42.8%
Vaccination status	**Vaccinated: 61.0% / Unvaccinated: 39.0%**

Age (years), n (%)			
Mean (SD)	**≥60**	**<75**	**≥75**
42.0 (13.5)	104 (9.7)	1052 (98.5)	16 (1.5)

Body Mass Index (kg/m^2), n (%)			
Mean (SD)	**≥25**	**<30**	**≥30**
26.5 (5.4)	520 (48.7)	836 (78.3)	230 (21.5)

Risk Factors for Severe COVID-19 Illness					
Number of Risk Factors[a]	**0**	**1**	**2**	**3**	**≥4**
	40.3%	33.3%	16.6%	6.7%	3.1%

Comorbidities with Prevalence ≥1%, n (%)	
Cardiovascular	15 (1.4)
Chronic lung disease	21 (2.0)
Diabetes mellitus	66 (6.2)
Hypertension	160 (15.0)
Cigarette smoker	170 (15.9)

Baseline Characteristics of SARS-CoV-2 Infection					
Serology Status, n (%)	**Negative**			**Positive**	
	261 (24.4)			**787 (73.7)**	
Baseline Viral Load (log_{10} Copies / mL)	**0**	**<4**	**≥4**	**<7**	**≥7**
	18.0%	**30.1%**	**68.1%**	**66.2%**	**31.9%**
Days Since First Symptom, n (%)	**≤3**			**>3**	
	785 (73.5)			**283 (26.5)**	

a. Risk Factors Include: Age ≥60, BMI >25 and Verbatim from pre-specified Medical History (Cigarette Smoker, Chronic Kidney Disease, Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence)
kg=kilogram, m=meter, mITT1=modified intent-to-treat 1, mL= milliliter, SD=Standard Deviation

>95% of PAXLOVID Treated Participants Completed Treatment in EPIC-SR

	PAXLOVID N=544 n (%)	Placebo N=531 n (%)
Participants who entered treatment	**544 (100)**	**531 (100)**
Completed treatment	521 (95.8)	510 (96.0)
Discontinued treatment for any reason	23 (4.2)	21 (4.0)
Adverse Event	10 (1.8)	5 (0.9)
Withdrawal by subject	7 (1.3)	11 (2.1)
Other	4 (0.7)	3 (0.6)
No longer meets eligibility criteria	2 (0.4)	2 (0.4)
Death	0	0
Lack of efficacy	0	0
Lost to follow-up	0	0
Pregnancy	0	0
Protocol deviation	0	0
Noncompliance with study drug	0	0

Full Analysis Set (FAS)

Favorable Trends in Subjective and Objective COVID-19 Endpoints
EPIC-SR, mITT1

PAXLOVID administered twice daily within 5 days of symptom onset resulted in:

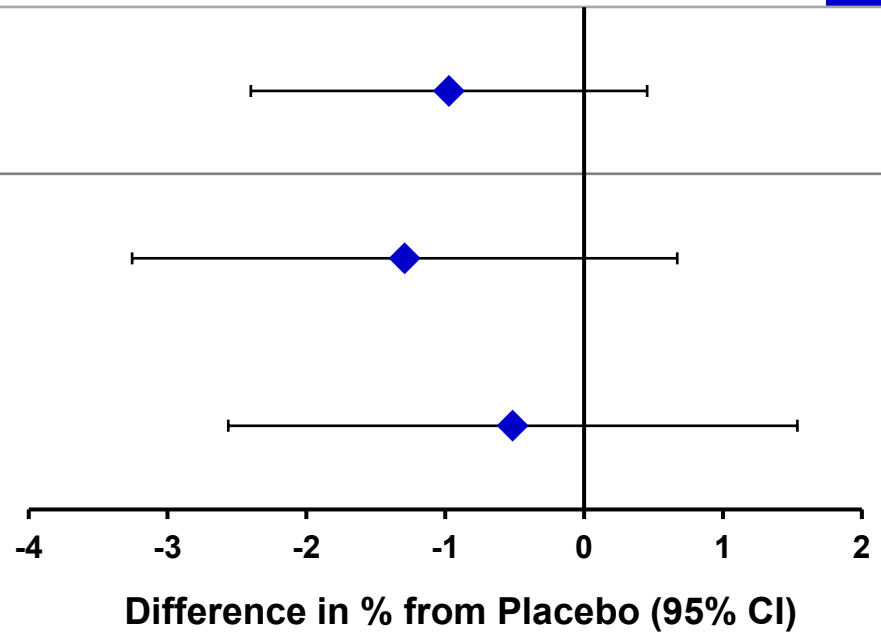
- **Reduction in median time to sustained alleviation of all targeted COVID-related symptoms from 14 days with placebo treatment to 13 days with Paxlovid treatment (p=0.5150)**
  - Primary efficacy endpoint not met
- **Similar 1-day improvement observed among vaccinated participants with risk factors for severe COVID (Hazard ratio p=0.8484)**
- **Reduction in the proportion of participants with COVID-19 related hospitalization or all-cause death through Day 28**
  - 57.6% (-1.3% difference, p=0.1970) and 35.8% (-0.51% difference, p=0.6233) relative risk reductions in vaccinated participants with risk factors for severe COVID-19 and in vaccinated or unvaccinated participants without risk factors for severe COVID-19
  - 1 death in a placebo treated participant (vaccinated with risk factors) through Day 28, no deaths in either treatment group during long-term follow-up
- **59% relative risk reduction compared to placebo in COVID-19 related medical visits**
- **Placebo-adjusted reduction of 0.87 log10 copies/mL (p<0.0001) in mean SARS-CoV-2 viral RNA concentration at 5 days after initiation of treatment**

mITT1=modified intent-to-treat 1

Reduction in COVID-19 Related Hospitalization or Death When Treatment is Initiated Within 5 Days of Symptom Onset

EPIC-SR, mITT1

Hospitalization or Death from Any Cause Through Day 28	PAXLOVID n/N (%)	Placebo n/N (%)	p-value
Overall	5/540 (0.935)	10/528 (1.907)	0.1815
Vaccinated with ≥1 Risk Factor	3/317 (0.952)	7/314 (2.245)	0.1970
No Risk Factors[a]	2/219 (0.920)	3/211 (1.433)	0.6233



a. Includes participants who were or were not vaccinated

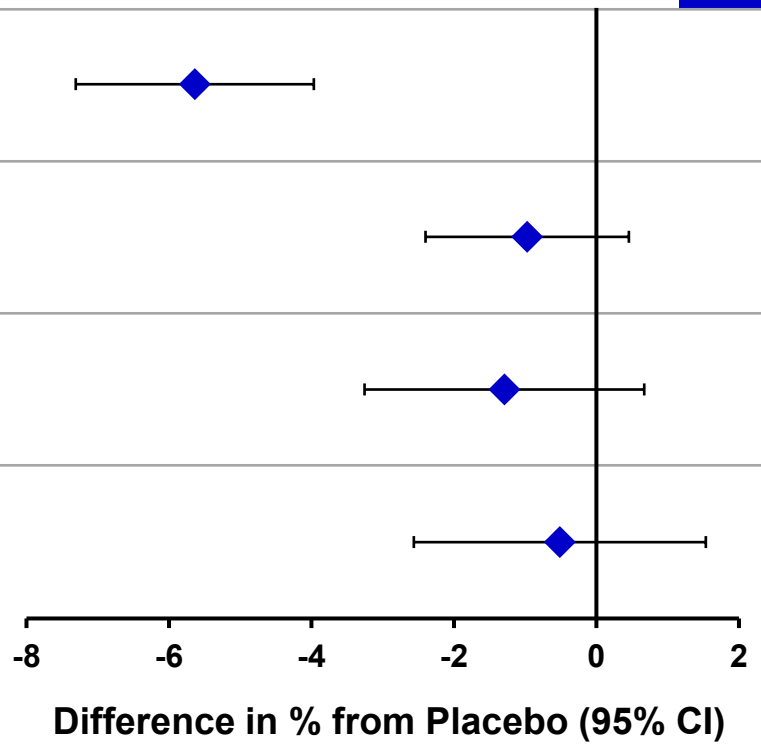
Kaplan-Meier Method; difference of the estimated proportions, 95% CI and p-value based upon normal approximation.

mITT1=modified intent-to-treat 1

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)	PAXLOVID n/N (%)	Placebo n/N (%)	p-value
EPIC-HR Secondary Analysis (mITT1)	9/977 (0.933)	64/989 (6.571)	<0.0001
EPIC-SR Overall	5/540 (0.935)	10/528 (1.907)	0.1815
Vaccinated with ≥1 Risk Factor	3/317 (0.952)	7/314 (2.245)	0.1970
No Risk Factors[a]	2/219 (0.920)	3/211 (1.433)	0.6233



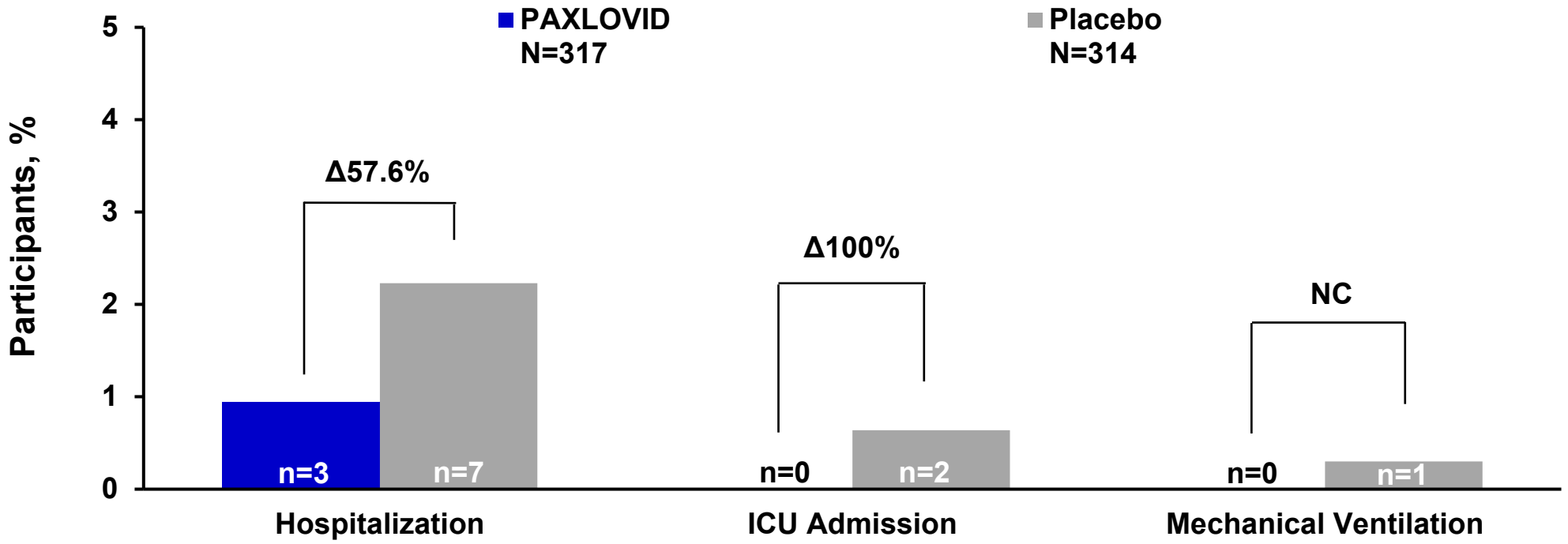
a. Includes participants who were or were not vaccinated

Kaplan-Meier Method; difference of the estimated proportions, 95% CI and p-value based upon normal approximation.

mITT1=modified intent-to-treat 1

Reduction in Risk of COVID-19 Hospitalization[a] in Vaccinated Participants with Risk Factors for Severe COVID-19

EPIC-SR, mITT1

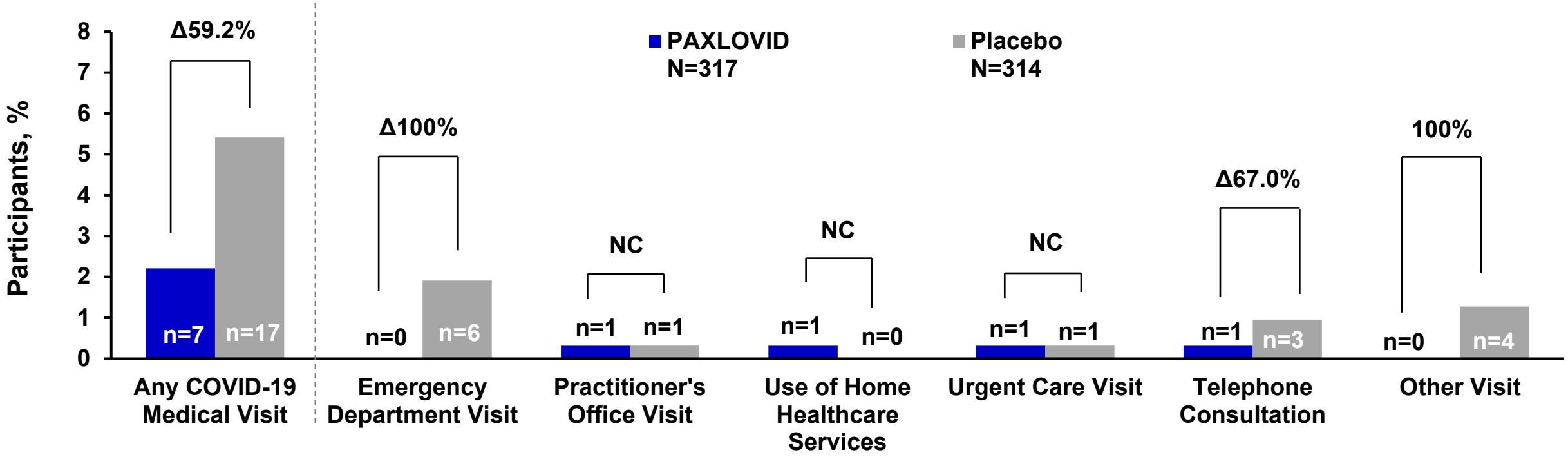


Favorable trend in reduction for risk of hospitalization and need for intensive care in vaccinated participants with risk factors for severe COVID-19 illness

a. Not limited through Day 28.
Δ = percent reduction with PAXLOVID compared with placebo.
ICU=intensive care unit, mITT1=modified intent-to-treat 1, NC=Not Calculated

Reduction in COVID-19–Related Health Care Utilization in Vaccinated Participants with Risk Factors for Severe COVID-19

EPIC-SR, mITT1[a]



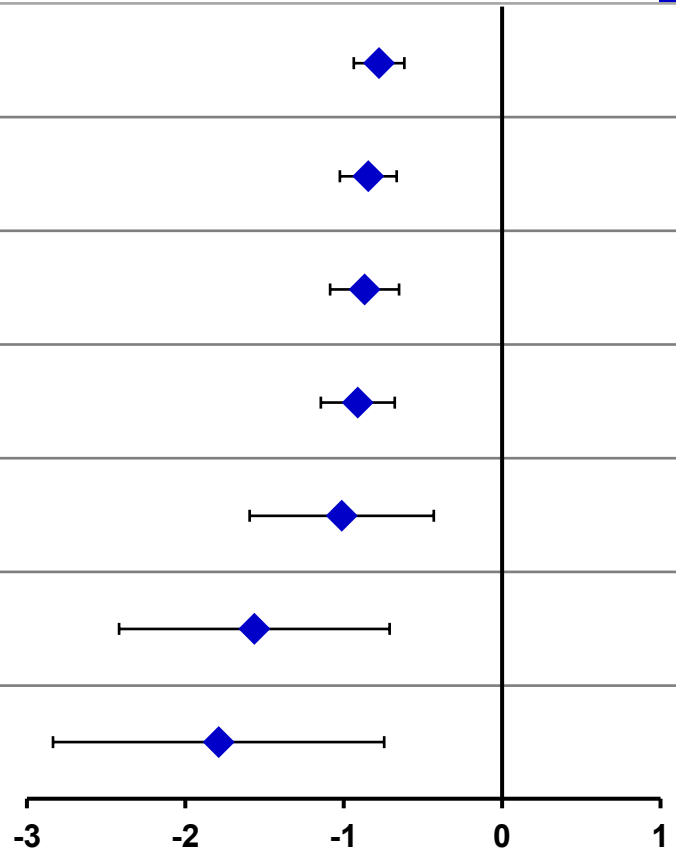
2.2% (7/317) with PAXLOVID and 5.4% (17/314) of participants who received placebo reported any COVID-19-related medical visit, corresponding to a 59% relative risk reduction with treatment

a. Not limited through Day 28.
Δ = percent reduction with PAXLOVID compared with placebo.
mITT1=modified intent-to-treat 1, NC=not calculated

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

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

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



Change from Baseline to Day 5 in Viral Load (log_{10} copies/mL) vs. Placebo (95% CI)

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

Effectiveness from Real-World Studies

John McLaughlin, PhD
Vice President
Global Medical Lead COVID and Influenza
Pfizer, Inc.

US Real-world Studies Support EPIC Results and Extend the Evidence for Omicron and Among Vaccinated

Study Characteristic	Ganatra et al.[1] *Clin Infect Dis* (No funding)	Dryden-Peterson et al.[2] *Ann Intern Med* (NIH funded)	Aggarwal et al.[3] *Lancet Infect Dis* (NIH funded)	Shah et al.[4] *CDC MMWR* (CDC funded)	Lewnard et al.[5] *Lancet Infect Dis* (CDC and NIH funded)
Endpoint	Hospitalization (30-day)	Hospitalization or death (14 & 28 days, respectively)	Hospitalization (28-day)	Hospitalization (30-day)	Hospitalization or death (30-day)
Index period (date of diagnosis or positive test)	1 Dec 2021 – 18 Apr 2022 (BA.1 & BA.2)	1 Jan – 17 Jul 2022 (BA.1, BA.2, & BA.4/5)	26 Mar – 25 Aug 2022 (BA.2 & BA.4/5)	1 Apr – 31 Aug 2022 (BA.2 & BA.4/5)	8 Apr – 7 Oct 2022 (BA.2 & BA.4/5)
Data source	TriNetX (>88M)	Mass General Brigham (1.5M)	Univ. of CO Health (largest system in CO)	EPIC Cosmos (>160M)	Kaiser Permanente S. Cal. (4.7M)
Population and analysis sample size	≥18 y n = 2260 (matched 1:1)	≥50 y n = 44,045	≥18 years n = 16,529 (matched ~1:1)	≥18 y n = 693,084	≥12 y n = 133,426 (matched 1:n)
% vaccinated (among analysis sample)	100% “vaccinated”	66% ≥3 doses	59% ≥3 doses	66% ≥2 mRNA doses	86% ≥2 doses
Control for bias	Propensity matching	Inverse probability treatment weights (IPTW)	Propensity matching & multivariable logistic models	Multivariable Cox PH	Matching & multivariable Cox PH

a. Effectiveness measured as 1 – relative risk.

1. Ganatra et al. *Clin Infect Dis* 2022. doi: 10.1093/cid/ciac673; 2. Dryden-Peterson et al. *Ann Intern Med* 2022. doi: 10.7326/M22-2141; 3. Aggarwal et al. *Lancet Infect Dis* 2023. doi: 10.1016/S1473-3099(23)00011-7; 4. Shah et al. *MMWR Morb Mortal Wkly Rep* 2022. doi: 10.15585/mmwr.mm7148e2; 5. Lewnard et al. Accepted at *Lancet Infect Dis*.

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Control for bias	Propensity matching	Inverse probability treatment weights (IPTW)	Propensity matching & multivariable logistic models	Multivariable Cox PH	Matching & multivariable Cox PH
Effectiveness[a] (95% CI) based on time of diagnosis or test	Within 5d of diagnosis: **60% (9, 80)**	Any time after pos. test: **44% (25, 58)** <3 doses: **81% (51, 92)** ≥3 doses: **31% (6, 50)**	Any time after diagnosis: **55% (38, 67)** 1-2 doses: **60% (21, 80)** ≥3 doses: **53% (26, 71)**	Within 5d of diagnosis: **51% (47, 54)** 2 mRNA doses: **50% (42, 58)** ≥3 mRNA doses: **50% (45, 55)**	Any time after positive test: **54% (7, 77)** ≥2 doses: **55% (7, 79)** ≥3 doses: **67% (24, 85)**
Effectiveness[a] (95% CI) based on time of symptom onset	Not applicable	Not applicable	Not applicable	Not applicable	Within 5d of *symptom onset*: **80% (34, 94)** ≥2 doses: **83% (30, 96)** ≥3 doses: **92% (52, 99)**

a. Effectiveness measured as 1 – relative risk.

1. Ganatra et al. *Clin Infect Dis* 2022. doi: 10.1093/cid/ciac673; 2. Dryden-Peterson et al. *Ann Intern Med* 2022. doi: 10.7326/M22-2141; 3. Aggarwal et al. *Lancet Infect Dis* 2023. doi: 10.1016/S1473-3099(23)00011-7; 4. Shah et al. *MMWR Morb Mortal Wkly Rep* 2022. doi: 10.15585/mmwr.mm7148e2; 5. Lewnard et al. Accepted at *Lancet Infect Dis*.

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a. Effectiveness measured as 1 – relative risk.

1. Ganatra et al. *Clin Infect Dis* 2022. doi: 10.1093/cid/ciac673; 2. Dryden-Peterson et al. *Ann Intern Med* 2022. doi: 10.7326/M22-2141; 3. Aggarwal et al. *Lancet Infect Dis* 2023. doi: 10.1016/S1473-3099(23)00011-7; 4. Shah et al. *MMWR Morb Mortal Wkly Rep* 2022. doi: 10.15585/mmwr.mm7148e2; 5. Lewnard et al. Accepted at *Lancet Infect Dis*.

Efficacy Conclusions and Safety from EPIC Randomized Clinical Trials

Jennifer Hammond, PhD
Vice President
Development Head Antivirals
Global Product Development, Pfizer Inc.

PAXLOVID is an Effective Treatment Option for High-risk Patients Irrespective of Prior Vaccination Status

PAXLOVID administered twice daily within 5 days of symptom onset results in:

- **85.8% (-5.6% difference, p<0.0001) reduction in hospitalization or all-cause death in EPIC-HR**
- **57.6% (-1.3% difference, p=0.1970) reduction hospitalization or all-cause death in vaccinated participants with risk factors for severe COVID-19 in EPIC-SR**
- **No deaths for PAXLOVID treated participants vs 16 in placebo treated participants**
- **Reduction in number of COVID-19 related medical visits**
- **Reductions in time to sustained alleviation and resolution of all targeted COVID-related symptoms in EPIC-HR**
- **Significant additional reduction in SARS-CoV-2 viral RNA concentration of ~0.8 - 1.8 $\log_{10}$ copies/mL at Day 5 in studies with Delta and Omicron predominance**
- **Real world data across multiple US studies confirm findings in 1) Omicron era; 2) Vaccinated patients and 3) CDC defined high risk groups**

Safety Presentation Topics

Overview of:

- **Adverse events**
- **Clinical laboratory and vital sign evaluations**
- **Post-marketing safety surveillance**

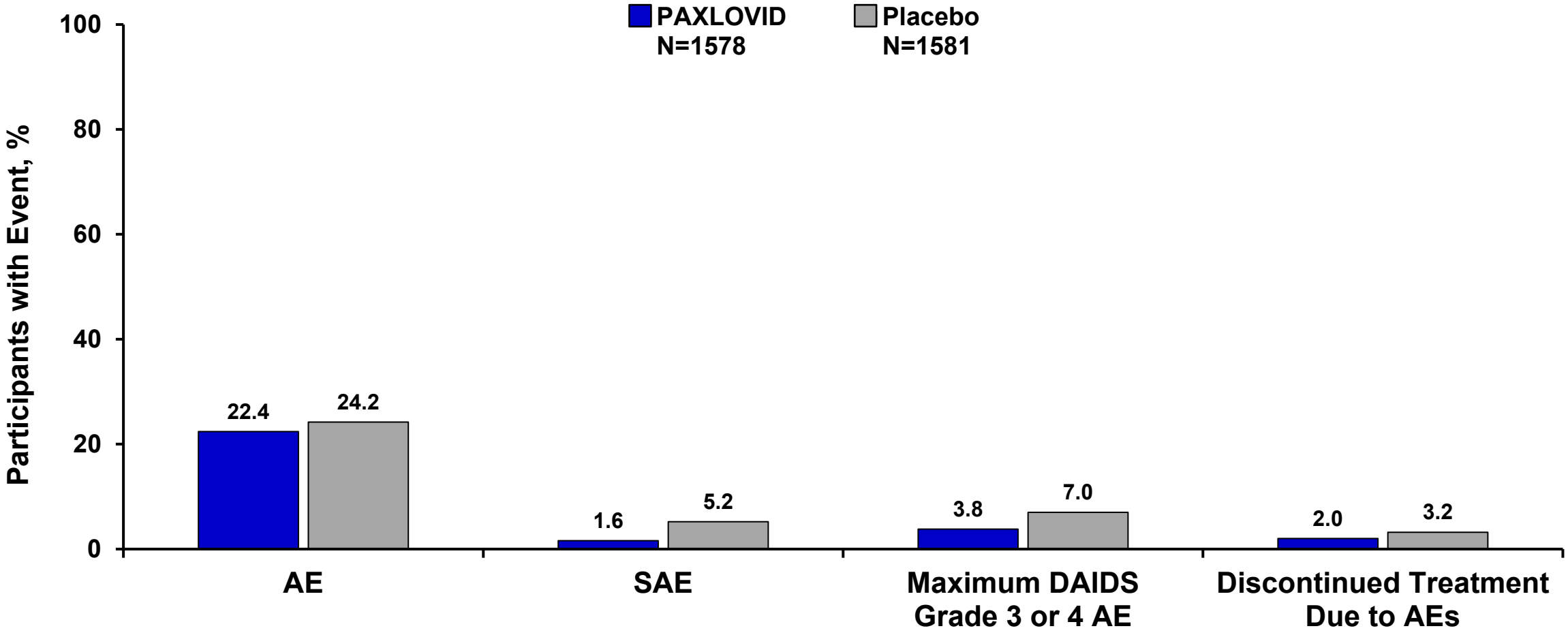
Overview of General Safety

- **Overall safety profile based on safety data from ~6300 participants (>3600 PAXLOVID treated) in 13 clinical studies**
  - 4 Phase 2/3 and 9 Phase 1
- **Consistent pattern of safety across studies in the integrated safety pool (EPIC-SR and EPIC-HR) and in various participant subgroups**
  - Majority (96%) of AEs, mild-moderate (DAIDS Grade 1 or 2) in severity
    - ≤2% incidence of SAEs or AEs leading to discontinuation of treatment
  - 16 deaths in total through 24 weeks of follow-up, all in placebo treatment group
  - No clinically meaningful changes in laboratory values, vital signs or ECG results
- **PAXLOVID has an acceptable safety profile that supports a positive benefit / risk assessment for the treatment indication being sought**

AE=Adverse Event; DAIDS=Division of AIDS; ECG=Electrocardiogram

Treatment Emergent Adverse Events

Pooled EPIC-SR and EPIC-HR, SAS



AE=Adverse Event; DAIDS=Division of AIDS; SAE=Serious Adverse Event; SAS=Safety Analysis Set

Most Frequent (≥1%) All-Causality AEs

Pooled EPIC-SR and EPIC-HR, SAS

AE Preferred Term	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)
Dysgeusia	**78 (4.9)**	**3 (0.2)**
Diarrhea	**53 (3.4)**	**32 (2.0)**
Nausea	32 (2.0)	35 (2.2)
ALT Increased	30 (1.9)	35 (2.2)
Fibrin D-dimer Increased	28 (1.8)	36 (2.3)
Headache	18 (1.1)	19 (1.2)
Vomiting	22 (1.4)	20 (1.3)
Creatinine Renal Clearance Decreased	19 (1.2)	20 (1.3)
AST Increased	17 (1.1)	18 (1.1)
COVID-19 Pneumonia	12 (0.8)	50 (3.2)
aPTT Prolonged	12 (0.8)	18 (1.1)
Pneumonia	4 (0.3)	20 (1.3)

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All-Causality SAEs, >1 Participant

Pooled EPIC-SR and EPIC-HR, SAS

SAE Preferred Term	PAXLOVID N=1578 n (%)	Placebo N=1581 n (%)
With Any SAE	26 (1.6)	82 (5.2)
COVID-19 Pneumonia	**10 (0.6)**	**44 (2.8)**
Pneumonia	2 (0.1)	13 (0.8)
COVID-19	2 (0.1)	8 (0.5)
Creatinine Renal Clearance Decreased	1 (0.1)	2 (0.1)
Dyspnea	1 (0.1)	3 (0.2)
Acute Respiratory Failure	0	5 (0.3)
Pneumonitis	0	5 (0.3)
Hypoxia	0	2 (0.1)
Interstitial Lung Disease	0	2 (0.1)
Pulmonary Embolism	0	2 (0.1)

SAE=Serious Adverse Event; SAS=Safety Analysis Set

No Laboratory, Vital Sign or ECG Related Safety Concerns or Precautions for Use in Special Populations

- **No clinically meaningful differences were observed between PAXLOVID and placebo groups with respect to hematology and clinical chemistry laboratory test results**
  - No potential Hy's Law cases identified in any treatment group through Study Day 34 (28 days post-treatment)
- **No clinically meaningful findings in vital sign measurements were observed in either treatment group**
- **PAXLOVID not associated with clinically meaningful changes in ECG results**
  - C-QTc analysis indicates that treatment with nirmatrelvir is not associated with clinically relevant QTc prolongation
- **No special precautions regarding safe use of PAXLOVID in any of the assessed participant sub-populations**
  - Age, gender, race, BMI, vaccination status, presence or number of risk factors for severe COVID-19

BMI=Body Mass Index, ECG=Electrocardiogram, PK=Pharmacokinetic, C-QTc= concentration-QTc, QTc=corrected QT interval

Has an Acceptable Safety Profile That Supports a Positive Benefit / Risk Assessment

- **Consistent pattern of safety in >3100 participants in the integrated safety pool (EPIC-SR and EPIC-HR) and in various participant subgroups**
  - Majority of AEs were mild-moderate in severity
  - Low incidence of SAEs or AEs leading to discontinuation of treatment
  - 16 deaths in total through 24 weeks of follow-up, all in placebo group
  - No clinically meaningful changes in laboratory values, vital signs or ECG results
- **Pharmacovigilance system operational for >1 yr and will continue to help monitor and guide safe use of PAXLOVID**

AE=Adverse Event; ECG=Electrocardiogram; SAE=Serious Adverse Event

Safety from Post-Marketing Surveillance

Lubna Merchant, MS, PharmD
Director, Risk Management Center of Excellence,
Worldwide Safety, Pfizer Inc.

Overview of Post-Marketing Spontaneous Reports Received from the US

- **PAXLOVID safety profile in the post-marketing setting is consistent with safety conclusions derived from the clinical program**
- **Majority of cases reported have been non-serious (93%) and reported listed ADRs or underlying COVID-19 infection**
- **Robust signal detection has supported labelling updates; most notably include:**
  - Updates to Warnings and Precautions to include hypersensitivity
  - Regular updates to the drug interaction table and contraindications list to support appropriate PAXLOVID use
  - Addition of ADRs to the label such as anaphylaxis

Ongoing and Active Pharmacovigilance and Pharmacoepidemiology

Pharmacoepidemiology Studies	• **2 studies in pregnant patients** • **Studies include pediatric patients**
Pharmacovigilance	• **Detect unexpected safety events rapidly** • Spontaneous report collection • Active follow-up • Frequent signal detection and evaluation
Proactive Risk Mitigation	• Labeling • Eligibility checklist • Educational materials • Drug interaction checker • Updated packaging presentation • Continuing education

Drug-Drug Interactions (DDIs)

- **DDIs with PAXLOVID are mainly due to:**
  - Ritonavir-mediated inhibition of CYP3A4, CYP2D6, and P-gp substrates
  - Potent CYP3A inducers which reduce the systemic levels of nirmatrelvir/ritonavir
- **PAXLOVID is contraindicated with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions, and with potent CYP3A inducers**
- **Concomitant use of PAXLOVID and certain drugs may result in potentially important DDIs which can be managed through:**
  - Dose reduction of the concomitant medication
  - Increased monitoring for adverse events or concomitant medication drug levels
  - Temporary discontinuation of concomitant medications or avoiding co-administration
- **The short duration of therapy is an inherent risk mitigation**
- **DDIs should be managed as described in the FactSheet and should be an important benefit vs. risk consideration**

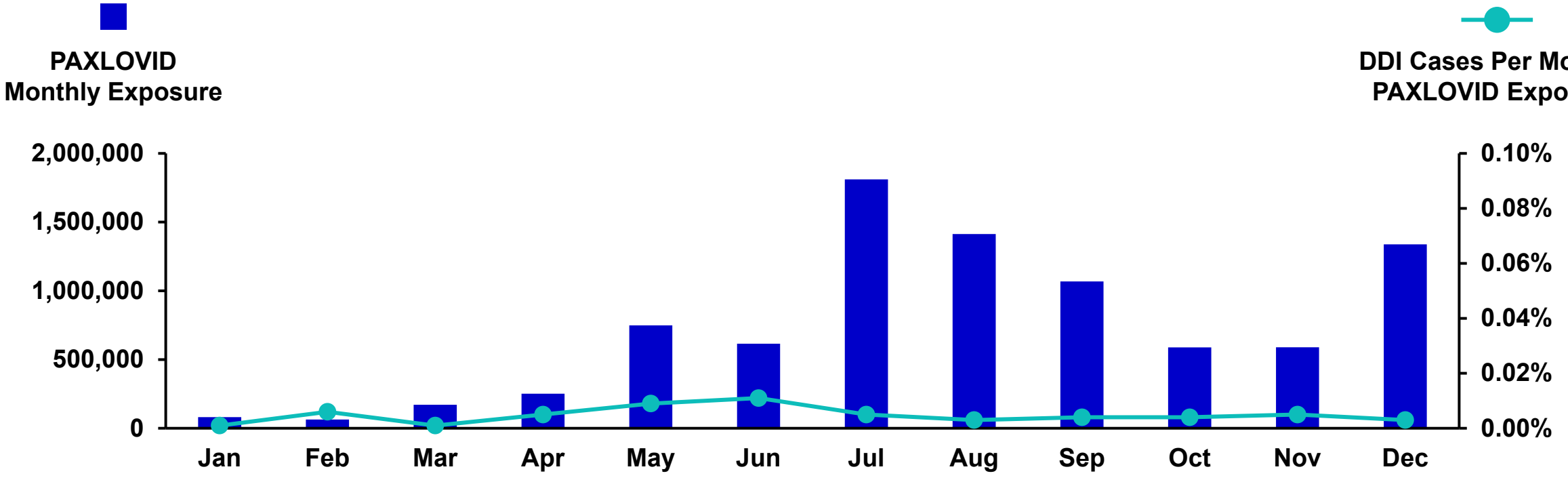
Risk Mitigation for Drug Interactions

Method of Risk Mitigation	Resources under EUA	Additional Resources under NDA
Communication and Outreach	• DHCP letters[a] • Social media and medical outreach	• Journal informational pieces • Publications on drug interactions with most prescribed US drugs
Point of Care Solutions	• HCP Fact Sheet • FDA Prescriber eligibility checklist[a] • Drug interaction tools (Pfizer, NIH, University of Liverpool)[a] • Computerized drug interaction checker programs used in community pharmacies[a]	• Alert box on outer packaging proposed • HCP USPI
HCP Education	• Drug interaction resource on Pfizer Medical Portal[a] • Drug-specific Medical Information Scientific Response Documents[a]	• Continuing Medical Education Grant • Prescribing awareness poster
Patient Education	• Patient, Parent and Caregiver Fact Sheet	• FDA approved patient labelling

a. Resources available under EUA will continue under NDA.

Reporting Rate of Drug Interactions in the US Post-Marketing Setting Remains Low

- **Amongst 8.6 M patient exposure, the overall cumulative reporting rate remains low (0.005%)**
- **427 cases reported a DDI, 83 serious cases**
  - Of the serious, 44 cases led to hospitalization, includes 2 fatal cases[a] (multiple co-morbidities)



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Number of Cases	1	4	2	12	67	69	88	49	39	24	28	44

a. Both patients had multiple co-morbidities, one died from COVID-19 and the other patient's cause of death was reported as Cardiac arrest following multiple events and interventions.
Data from January-December 2022

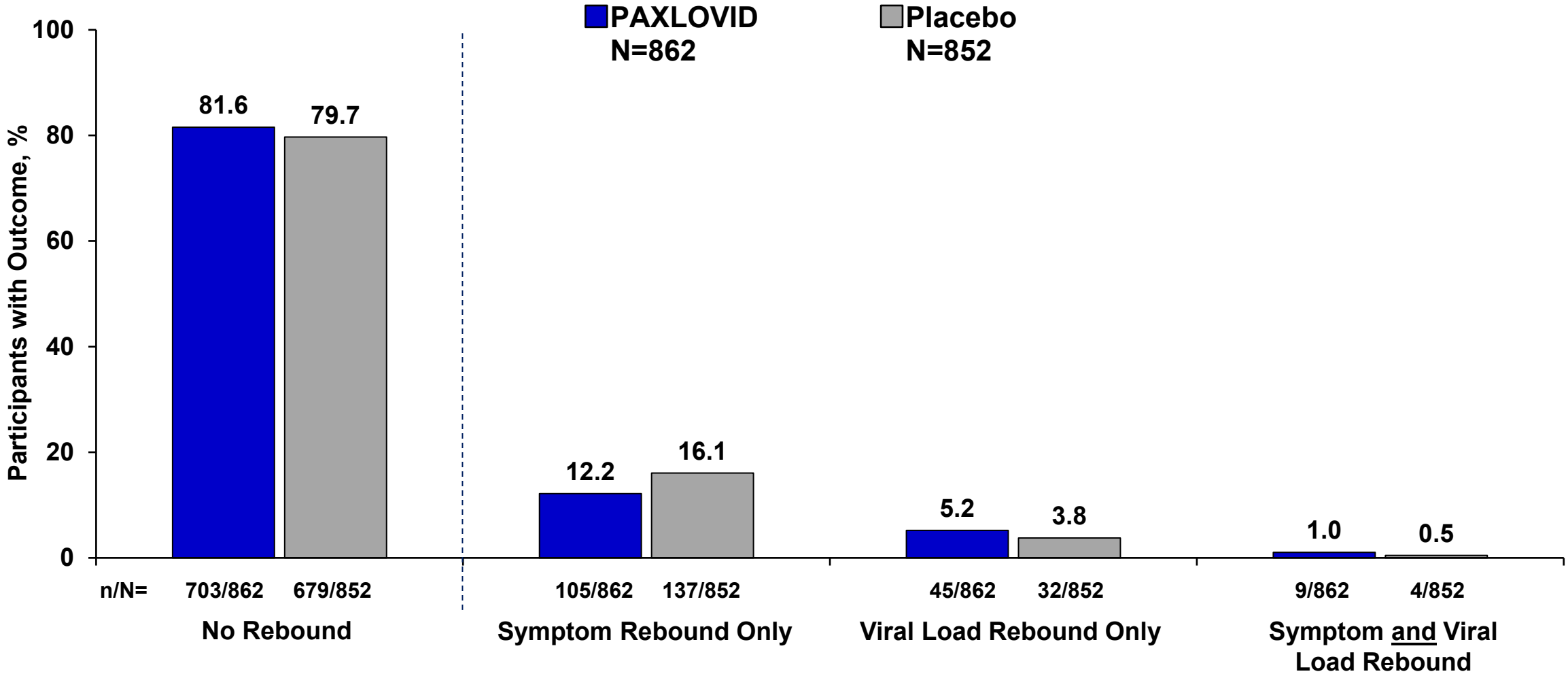
COVID-19 Rebound, Continued Development, and Conclusions

James Rusnak, MD, PhD
Senior Vice President
Chief Development Officer,
Internal Medicine, Anti-infectives, and Hospital
Global Product Development, Pfizer Inc.

COVID-19 Rebound

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

Symptom[a] and Viral Load[b] Rebound Occurrence in EPIC-HR is Low and Similar Across Treatment Groups



1. Deo et al. Ann Intern Med 2023. doi:10.7326/M22-2381 (Viral rebound on or after Day 5 and Symptom rebound any time after Day 0)

a. Symptom rebound defined as any improvement in COVID-19 signs/symptoms and subsequently worsened (total symptom score increased by ≥4)

b. Rebound in viral load defined as: 1) if VL<LLOQ at Day 5, Day 10 or 14 VL ≥ 3.0 $\log_{10}$ copies/mL; (2) if VL≥LLOQ at Day 5, Day 10 or 14 VL increases by ≥0.5 $\log_{10}$ copies/mL from Day 5, AND the Day 10 or 14 VL has to be ≥3.0 $\log_{10}$ copies/mL

Incidence of Rebound from Literature Consistent with Observations from EPIC-HR

Source	Viral Load Rebound or SARS-CoV-2 Rapid Antigen Test Positivity	Symptom Relapse
Clinical Trial Evidence		
ACTIV-2 placebo cohort (NIH)[1]	Increase of 0.5 and ≥3.0 log_{10} RNA copies/mL: Placebo 20% (53/261) Increase of 0.5 and ≥5.0 log_{10} RNA copies/mL: **Placebo 6.5% (17/261)**	**Placebo: 26% (148/563)** 4-point worsening after symptom improvement
Real World Evidence		
Wang *et al* (TriNetX)[2]	30 Day PAXLOVID: 7.1% (159/2226) 30 Day Molnupiravir: 8.5% (189/2226)	30 Day PAXLOVID: 7.6% (168/2226) 30 Day Molnupiravir: 8.0% (178/2226)
Ranganth *et al* (Mayo Clinic)[3]	Not Available	30 Day PAXLOVID: 0.8% (4/483)

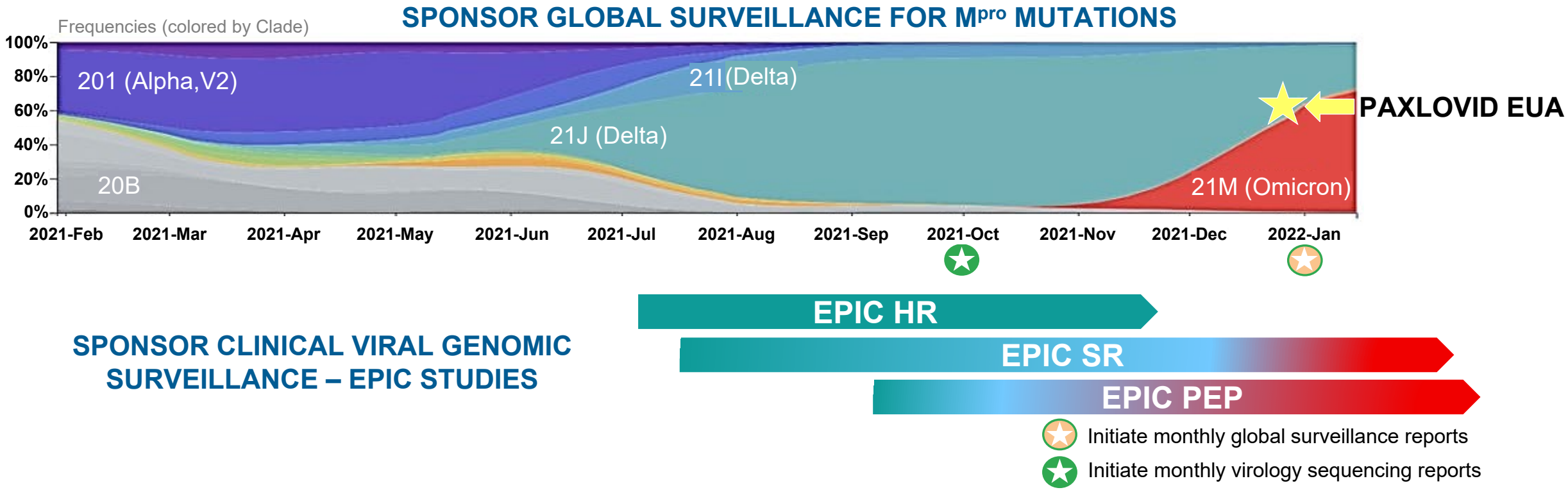
1. Deo et al. Ann Intern Med 2023. doi:10.7326/M22-2381 (Viral rebound on or after Day 5 and Symptom rebound any time after Day 0)
2. Wang et al, pre-print, Jun 2022
3. Ranganath et al. CID 2023. doi.org/10.1093/cid/ciac481

CDC Health Advisory: COVID-19 Rebound After PAXLOVID Treatment

"…**A brief return of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status.** Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease..."

COVID-19 Rebound After Paxlovid Treatment (cdc.gov), May 24, 2022

Surveillance Shows No Evidence of Clinical Resistance in EPIC-HR, SR, or PEP Study Participants or Through Global Monitoring[a]



- **No hospitalization or death in EPIC-HR, SR and PEP participants were associated with mutations with reduced in vitro susceptibility to nirmatrelvir discovered in Pfizer or in the literature[b]**
- One in vitro resistance mutation, E166V, emerged on treatment in 3 patients from EPIC-HR, SR, and PEP. **None of these patients experienced hospitalization or death[c]**

a. Clinical resistance is defined as the emergence or preexistence of resistance mutations that lead to treatment failure.
b. Internal Pfizer data and Zhou et al, bioRxiv 2022; Iketani et al, bioRxiv 2022
c. Emergent mutation reporting ≥10% AAFREQ, absent at baseline, PAX incidence ≥2.5x Placebo, with ≥3 more occurrences on PAXLOVID.

PAXLOVID (nirmatrelvir / ritonavir)
Continued Development and Conclusions

Further Study to Guide Use of PAXLOVID in Special Populations

- **EPIC-IC: Immunocompromised participants who are not hospitalized (NCT05438602)**
  - DB RCT – 5, 10, 15 days of PAXLOVID; virologic and clinical endpoints
- **Long-COVID studies**
  - NIH/NHLBI/NIAID RECOVER program; studies for both treatment and prevention
  - Clinical research collaborations with multiple academic institutions
- **Retreatment in patients who have symptomatic COVID-19 rebound (NCT05567952)**
  - 5 days PAXLOVID vs. placebo
- **PK Studies in special populations**
  - Adolescent and pediatric patients (EPIC-Peds / NCT05261139)
  - Patients with severe renal impairment (EPIC-SRI / NCT05487040)
  - Patients who are pregnant (C4671035 / NCT05386472) or lactating (C4671039 / NCT05441215)

Benefit-Risk and Conclusions

- **Based upon efficacy and safety data from EPIC-HR and supportive EPIC-SR and EPIC-PEP studies**
  - Efficacy against hospitalization or death in both unvaccinated and vaccinated patients who are at increased risk for severe COVID-19 illness – similar reduction seen across patient subgroups
  - In vitro potency demonstrated across all known viral variants to date
  - Safe and well tolerated
- **Efficacy and safety further supported by a growing body of real-world evidence (14M patients globally with 10M in US) – confirming effectiveness against Omicron strains regardless of vaccination status**
- **Completion of planned/ongoing studies and robust ongoing pharmacovigilance and surveillance for viral resistance will further enable the safe use of the product**
- **Approval of the New Drug Application for treatment of mild-to-moderate COVID-19 disease in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, is warranted**