Effect of Nirmatrelvir/Ritonavir versus Placebo on COVID-19–Related Hospitalizations and Other Medical Visits*

Presented by Edward Weinstein[1]

Jennifer Hammond,[1] Heidi Leister-Tebbe,[1] Annie Gardner,[2] Paula Abreu,[3] Weihang Bao,[3] Wayne Wisemandle,[4] Wajeeha Ansari,[5] Abraham Simón-Campos,[6] Rienk Pypstra,[3] James M. Rusnak[7]

[1]Global Product Development, Pfizer Inc, Collegeville, PA, USA; [2]Global Product Development, Pfizer Inc, Cambridge, MA, USA; [3]Global Product Development, Pfizer Inc, New York, NY, USA; [4]Global Product Development, Pfizer Inc, Lake Forest, IL, USA; [5]Patient & Health Impact, Pfizer Inc, New York, NY, USA; [6]Köhler and Milstein Research/Agustín O'Horán Hospital, Mérida, Yucatan, Mexico; [7]Global Product Development, Pfizer Inc, Tampa, FL, USA

Forum for Collaborative Research; November 2, 2023; Washington, DC, USA

*Presented at IDWeek 2022, Abstract Available in *Open Forum Infectious Diseases*, Volume 9, Issue Supplement_2, December 2022, ofac492.047

Speaker Disclosure

- Edward Weinstein is an employee of and holds stock/stock options in **Pfizer Inc**.

Background

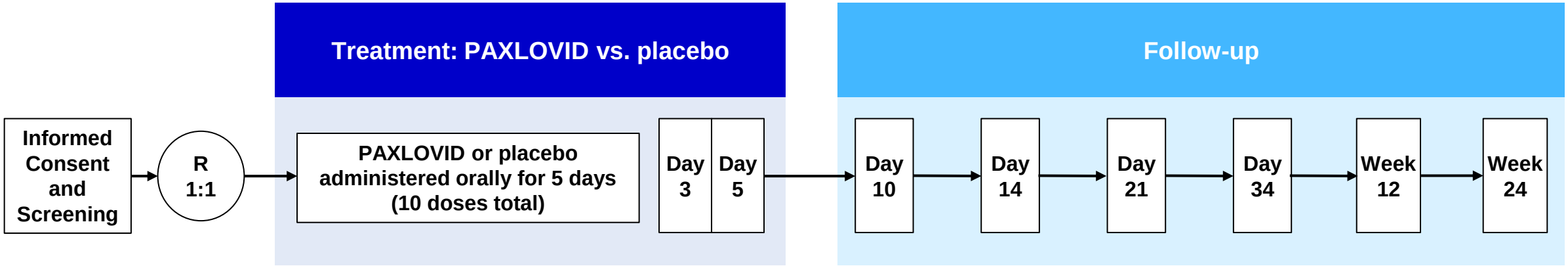
- Nirmatrelvir is a potent inhibitor of the SARS-CoV-2 main protease (M^{pro}) co-administered with low dose ritonavir to increase nirmatrelvir plasma concentrations.[1,2]
- Approved for the treatment of mild-to-moderate COVID-19 in adults and authorized under EUA for pediatric patients (12 years of age and older weighing at least 40 Kg) who are at high risk for progression to severe disease.[1]
- Previously published results of the primary endpoint from EPIC-HR (NCT04960202) demonstrated an 86% relative risk reduction against COVID-19–related hospitalization or all-cause death through Day 28 when treatment was initiated within 5 days of symptom onset.[3,4]
- Additional analyses from EPIC-HR show a reduction in duration and severity of COVID-19 signs and symptoms compared to placebo in patients at high risk of progression to severe disease[5]

Here, we review additional secondary endpoints from EPIC-HR including overall COVID-19–related healthcare utilization

1. Pfizer Inc. Fact sheet for healthcare providers: Emergency use authorization for PAXLOVID™. 2022.
2. Owen D et al. Science. 2021 Dec 24;374(6575):1586-1593
3. Hammond J, et al. N Engl J Med. 2022;386(15):1397-1408.
4. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-submission-new-drug-application-us-fda
5. Hammond et al. Poster presented at IDWeek 2022. Poster 1156, Submitted for publication

Study Design: 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 Cancer, Cigarette Smoker, Cardiovascular Disorder, Chronic kidney Disease, Chronic Lung Disease, Diabetes Mellitus, Device Dependence, HIV Infection, Hypertension, Immunosuppression, Neurodevelopmental Disorder and Sickle Cell Disease

Study Population and Endpoints

Phase 2/3, double-blind study
(EPIC-HR; NCT04960202)

Patients

- ✓ ≥18 years of age
- ✓ Confirmed SARS-CoV-2 infection
- ✓ Symptom onset ≤5 days before randomization
- ✓ ≥1 characteristic or condition associated with high risk of progression to severe COVID-19
- ✗ Previous confirmed SARS-CoV-2 infection
- ✗ Prior receipt of convalescent COVID-19 plasma or SARS-CoV-2 vaccine
- ✗ Anticipated hospitalization need within 48 hours

RANDOMIZE 1:1

TREATMENT
Days 1–5
(10 doses total)

- **Nirmatrelvir 300 mg + ritonavir 100 mg (n=1120)**
- **Placebo (n=1126)**

SAFETY FOLLOW-UP through Day 34

LONG-TERM FOLLOW-UP Through Week 24

Primary endpoint

Proportion of patients with COVID-19–related hospitalization or all-cause death through Day 28

Secondary endpoints presented herein

- Details of COVID-19–related hospitalization, including frequency, duration, ICU admissions, and need for mechanical ventilation
- Number of COVID-19–related medical visits
- Use of Oxygen support

EPIC-HR=Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients; ICU=intensive care unit.

Patient Dispositions and Baseline Characteristics

- **Disposition**
  - Of the 2246 patients who entered the study, 2092 (93.1%) completed study treatment.
    - The most common reasons for discontinuation of study treatment were adverse events (2.1% and 4.2% in the nirmatrelvir/ritonavir and placebo groups, respectively) and withdrawal by subject (2.9% and 2.4%).
- **Baseline demographic and clinical characteristics were similar between groups (Table).**

Demographics and Characteristics	Full Analysis Set		
	Nirmatrelvir/ ritonavir (n=1120)	Placebo (n=1126)	Total (N=2246)
Median (range) age, y	45.0 (18.0–86.0)	46.5 (18.0–88.0)	46.0 (18.0–88.0)
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Ethnicity, n (%)			
White	800 (71.4)	808 (71.8)	1608 (71.6)
Black	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	160 (14.2)	314 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
First symptom ≤3 days before treatment, n (%)	754 (67.3)	735 (65.3)	1489 (66.3)
COVID-19 mAb treatment not received/not expected to receive, n (%)	1050 (93.8)	1056 (93.8)	2106 (93.8)
Positive baseline serology, n (%)	581 (51.9)	568 (50.4)	1149 (51.2)
Common risk factors for severe COVID-19 at baseline			
BMI ≥25 kg/m^2	899 (80.3)	908 (80.6)	1807 (80.5)
Cigarette smoking	428 (38.2)	448 (39.8)	876 (39.0)
Hypertension	359 (32.1)	381 (33.8)	740 (32.9)
Diabetes	136 (12.1)	138 (12.3)	274 (12.2)

BMI=body mass index; mAb=monoclonal antibody.

COVID-19–Related Hospitalization and All-Cause Mortality

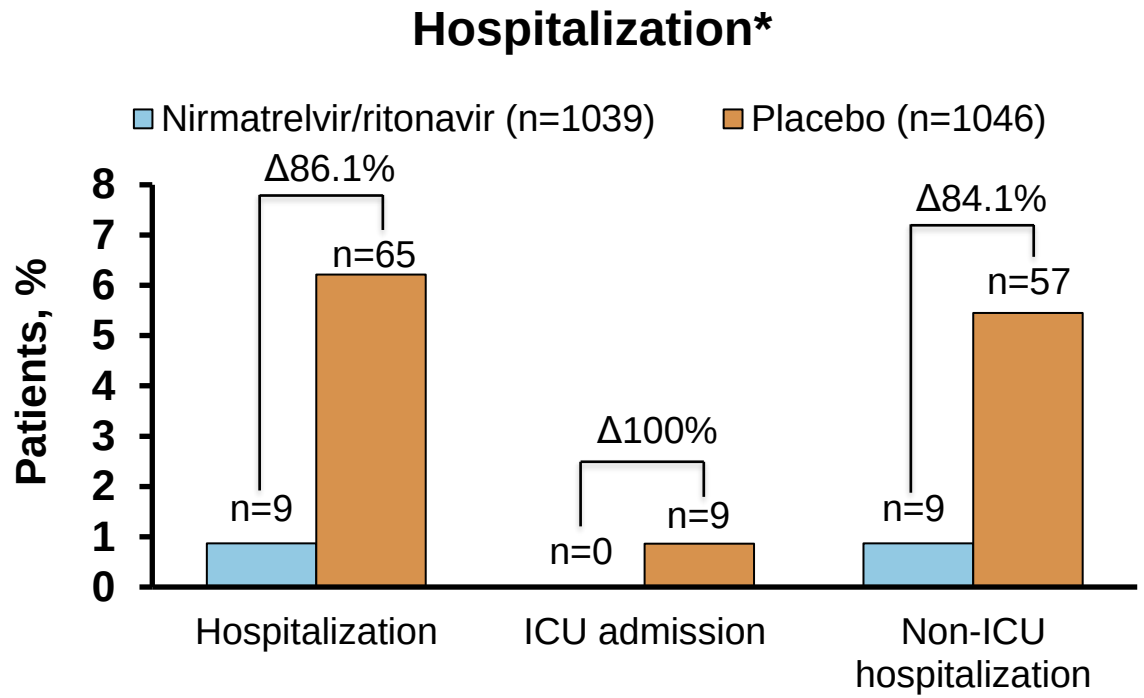
	mITT1 Population (Treated ≤5 days after COVID-19 onset)	
	Nirmatrelvir/ritonavir (n=1039)	Placebo (n=1046)
Patients with primary event through Day 28, n (%)	9 (0.87)	66 (6.31)
Hospitalized for COVID-19, n (%)	9 (0.87)	65 (6.21)
Died, n (%)	0	12 (1.15)
Estimated proportion (95% CI), %	0.88 (0.46, 1.68)	6.40 (5.06, 8.08)
Difference from placebo (SE)	−5.52 (0.82)	
P value	<0.0001	
Patients who died through Week 24, n (%)	0	15 (1.4)
P value	<0.0001	

Fewer patients in the nirmatrelvir/ritonavir group experienced COVID-19–related hospitalizations or all cause mortality compared to placebo:

- 86% RRR in COVID-19-related hospitalization and all cause mortality through Day 28
- 100% RRR in all cause mortality through Week 24

mITT1=modified intent-to-treat 1; SE=standard error; RRR-relative risk reduction.

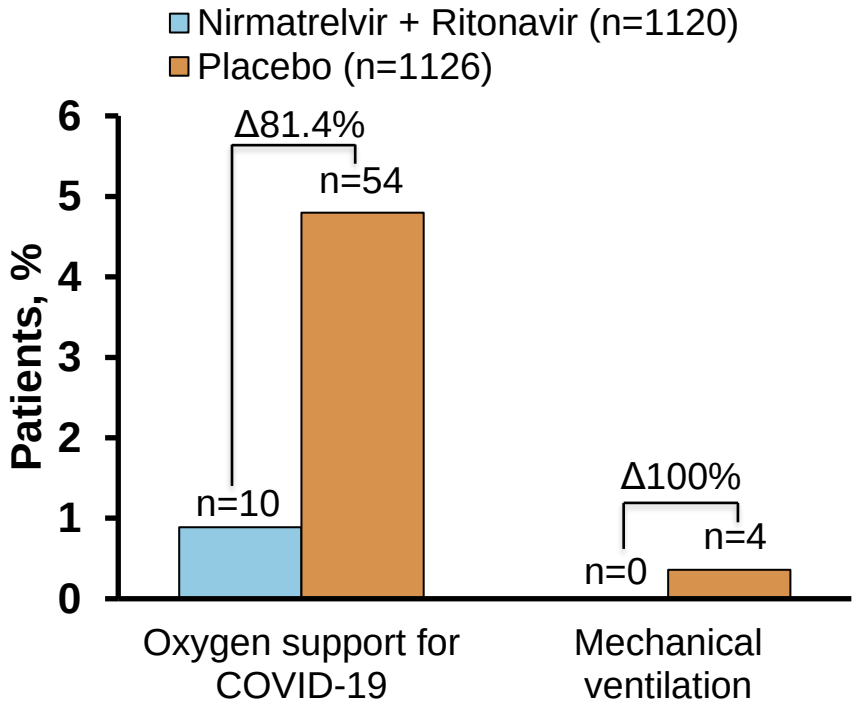
COVID-19–Related Hospitalization (mITT1)



- Fewer hospitalizations were reported among those who received nirmatrelvir/ritonavir compared with placebo.
  - No patients in the nirmatrelvir/ritonavir group and 9 patients in the placebo group were admitted to the ICU.
  - Mean days of hospitalization per 100 patients was significantly reduced among nirmatrelvir/ritonavir treated patients
- Among hospitalized participants with known discharge status, 100% of those who received nirmatrelvir/ritonavir were discharged to home self-care vs 52.9% of those receiving placebo.

*Not limited through Day 28.
Δ = percentage reduction with nirmatrelvir/ritonavir compared with placebo.
ICU=intensive care unit; mITT1=modified intent-to-treat 1

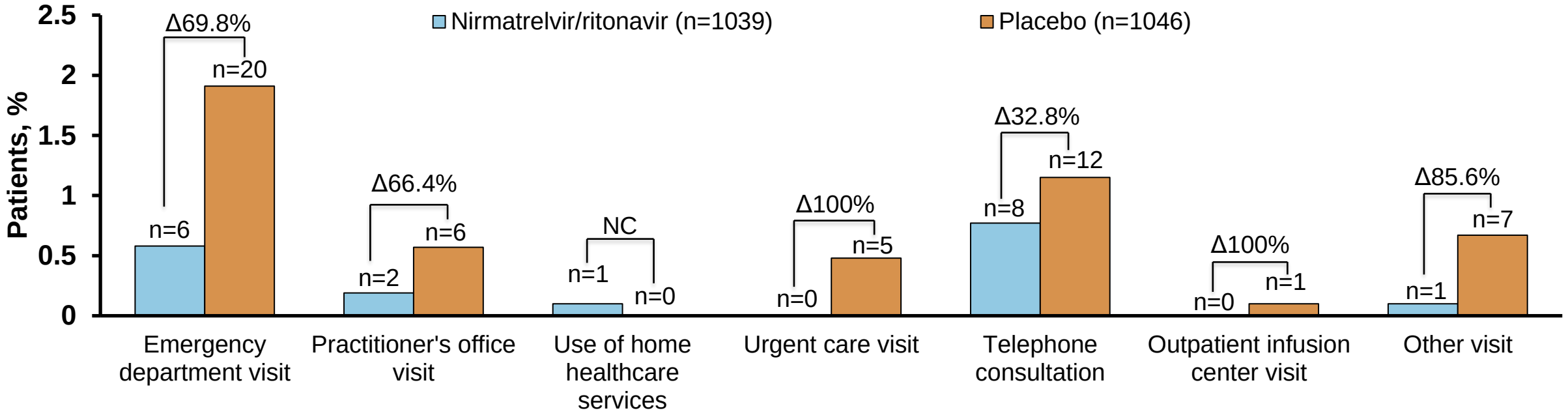
Patients who Received Oxygen Supplementation for COVID-19



- 81% RRR in requirement for oxygen support for COVID-19.
- None of the patients in the nirmatrelvir/ritonavir group vs 4 patients in the placebo group received mechanical ventilation.

Δ = percentage reduction with nirmatrelvir/ritonavir compared with placebo; RRR-relative risk reduction..

Other COVID-19–Related Medical Visits (mITT1)*

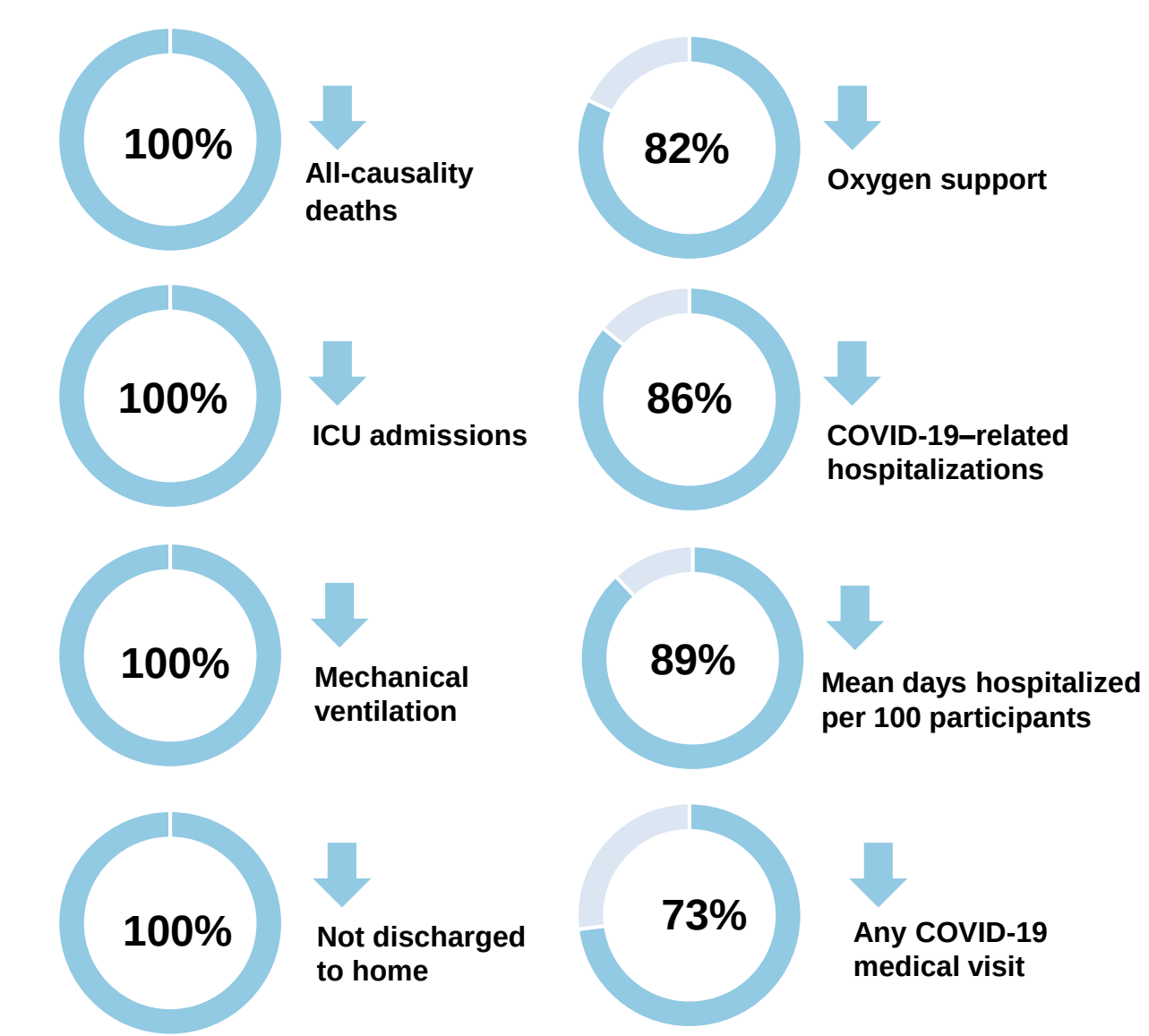


- Through Day 34, fewer patients in the nirmatrelvir/ritonavir group reported COVID-19–related medical visits compared to placebo.
  - 2.2% (23/1039) with nirmatrelvir/ritonavir and 8.1% (85/1046) of patients who received placebo reported any COVID-19–related medical visit, corresponding to a 73% RRR ($p<0.0001$) with treatment

*Not limited through Day 28.
Δ = percentage reduction with nirmatrelvir/ritonavir compared with placebo.
NC=not calculated; mITT1=modified intent-to-treat 1; RRR-relative risk reduction.

Conclusions

- Nirmatrelvir/ritonavir significantly reduced COVID-19 related hospitalizations and all-cause mortality in unvaccinated patients at high risk of progression to severe COVID-19 when treatment was initiated within 5 days of symptom onset
- Treatment with nirmatrelvir/ritonavir reduced COVID-19–related healthcare utilization compared with placebo-treated patients.



ICU=intensive care unit

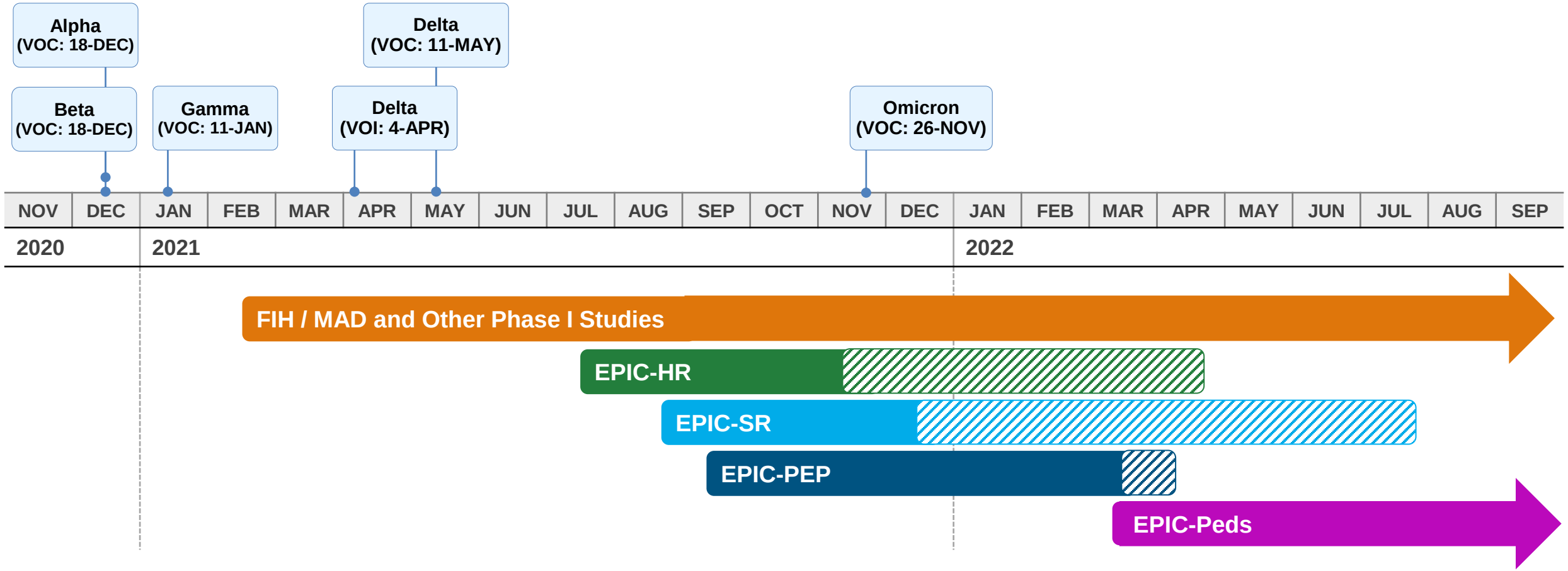
Acknowledgments

- Thank you to the patients who participated in the trial, investigators, and their study teams.
- Thank you to Jennifer Hammond and the Paxlovid study team for allowing me to present these study results.
- This study was sponsored by Pfizer Inc.

Back Up Slides

PAXLOVID Development Program

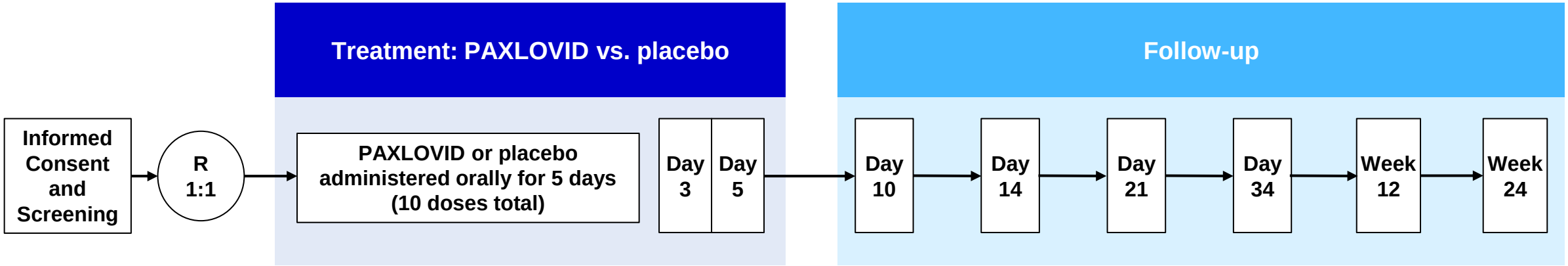
Safety and Efficacy Evaluated in >6000 Participants in 21 Countries



WHO, Oct 2021 Variants of Interest / Variants of Concern

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

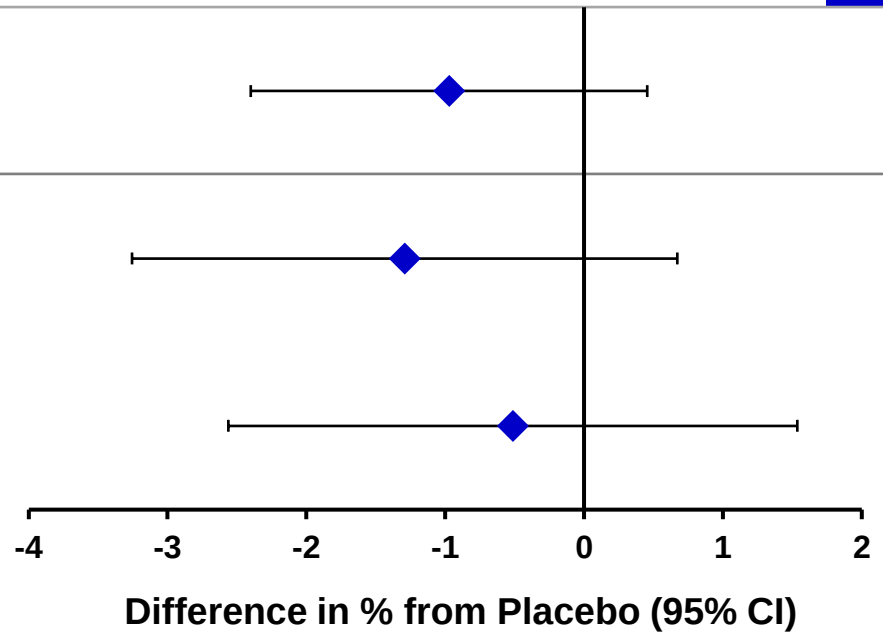
Day 28 Primary Endpoint
Time to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28

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)

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



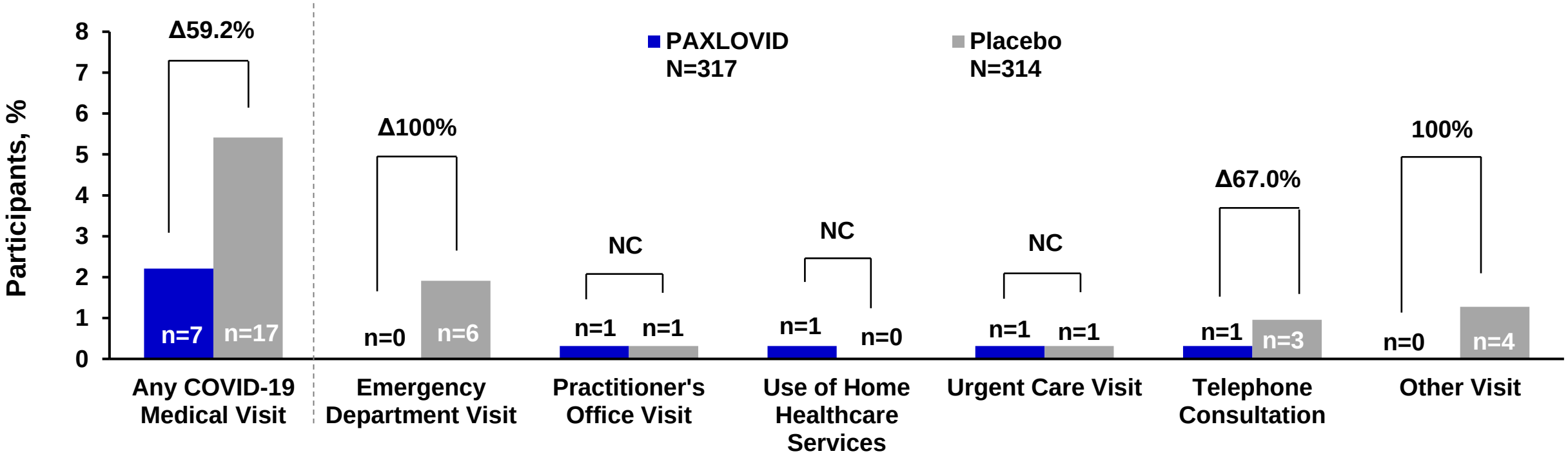
a. Includes participants who were or were not vaccinated

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 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