1156

Sustained Alleviation and Resolution of Targeted COVID-19 Symptoms With Nirmatrelvir/Ritonavir Versus Placebo

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BACKGROUND AND OBJECTIVES

- More than 600 million cumulative cases and 6.5 million deaths due to COVID-19 have been reported globally.[1]
- Severe cases of COVID-19 are associated with hospitalization, intensive care unit admission, invasive mechanical ventilation, or death.[2,3]
- Nirmatrelvir, a potent inhibitor of the SARS-CoV-2 3-chymotrypsin-like cysteine protease (M^{pro}), is an oral antiviral COVID-19 treatment that is coadministered with pharmacokinetic-boosting agent ritonavir (nirmatrelvir/ritonavir; PAXLOVID™, Pfizer Inc) and approved in the United States under emergency use authorization.[4,5]
- EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) was a phase 2/3 study evaluating nirmatrelvir/ritonavir 300 mg/100 mg twice daily in adults with mild to moderate COVID-19 at increased risk of progression to severe disease.[5]
  - Previously published results from EPIC-HR demonstrated an 88% relative risk reduction against COVID-19-related hospitalization or all-cause mortality through Day 28 when treatment was initiated within 5 days of symptom onset.[5]
- Here, we report additional secondary endpoints from EPIC-HR including time to sustained symptom alleviation and time to sustained symptom resolution through Day 28 in nonhospitalized symptomatic adult patients with COVID-19 who are at an increased risk of progression to severe disease.

METHODS

- In this phase 2/3 double-blind study (NCT04960202), eligible adults 18 years or older were randomized 1:1 to receive nirmatrelvir/ritonavir 300 mg/100 mg or placebo every 12 hours for 5 days (10 doses total).
- Patients were eligible for the study if they had confirmed SARS-CoV-2 infection from a specimen collected within 5 days of randomization, initial onset of COVID-19 signs/symptoms within 5 days before the day of randomization, ≥1 prespecified COVID-19 sign/symptom on the day of randomization, and ≥1 characteristic or underlying prespecified medical condition associated with increased risk of developing severe COVID-19 and had not received or were not expecting to receive any dose of a COVID-19 vaccine before the Day 34 visit.
- Efficacy endpoints were assessed as of the date of last patient last visit (April 26, 2022) for the following populations described in **Table 1**. The results presented herein focus on the modified intent-to-treat 1 (mITT1) population; in general, similar results were obtained for the mITT and mITT2 analysis sets.

Table 1. Analysis Populations

Population	Definition
mITT	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated within 3 days of COVID-19 onset.
mITT1	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
mITT2	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, including those who did or were expected to receive therapeutic mAbs.

mAb=monoclonal antibody; mITT=modified intent-to-treat; mITT1=modified intent-to-treat 1; mITT2=modified intent-to-treat 2.

- A subset of the full signs/symptoms collected were identified as "targeted" signs/symptoms and were included in the analyses. The targeted signs and symptoms attributable to COVID-19 were evaluated per prespecified US Food and Drug Administration guidelines[6] and included cough, shortness of breath or difficulty breathing, fever (documented temperature ≥38°C [100.4°F]) or subjective fever, feeling feverish, chills or shivering, fatigue (low energy or tiredness), muscle or body aches, diarrhea (loose or watery stools), nausea (feeling like you wanted to throw up), vomiting (throw up), headache, sore throat, stuffy or runny nose, loss of smell, and loss of taste (**Figure 1**).
- Patients logged the presence and severity on 3- or 4-point scales of the 15 prespecified COVID-19 signs/symptoms at approximately the same time daily from Day 1 (before dose) through Day 28 using an electronic handheld device.
- Study outcomes are described in **Table 2**.

Table 2. Description of Sustained Alleviation and Sustained Resolution of All Targeted COVID-19 Signs/Symptoms

Outcome	Definition
Sustained alleviation	• The event occurring on the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry were scored as mild or absent AND all symptoms scored mild or absent at study entry were scored as absent. • The first day of the 4 consecutive-day period was considered the First Event Date.
Sustained resolution	• The event occurring when all targeted symptoms were scored as absent for 4 consecutive days. • The first day of the 4 consecutive-day period was considered the First Event Date.

METHODS (continued)

- Times to sustained alleviation and resolution of all targeted signs/symptoms were assessed through Day 28 using the following analytical methods:
  - A Cox proportional hazard regression model where the estimate of the hazard ratio for treatment (nirmatrelvir/ritonavir vs placebo), its confidence interval (CI), and p-value were assessed.
  - Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves provided the median, quartiles, and range for each treatment group.
  - All missing efficacy data at baseline except for time to event endpoints were treated as mild. A baseline observation carried forward approach was used for missing data for participants discontinued due to an adverse event or lack of efficacy. The last observation carried forward method was used for other missing data.
- Individual signs/symptoms were compared between groups using descriptive analyses.

RESULTS

- Of the 2246 patients enrolled in EPIC-HR, 2085 (nirmatrelvir/ritonavir 300 mg/100 mg, n=1039; placebo, n=1046) met criteria for the mITT1 population.
- Demographic and baseline clinical characteristics within the mITT1 population were similar between the nirmatrelvir/ritonavir and placebo groups (**Table 3**).

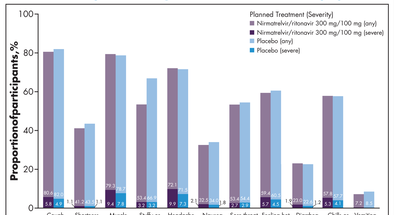
Table 3. Demographics and Baseline Characteristics (mITT1 Analysis Set)

Characteristic	Nirmatrelvir/Ritonavir 300 mg/100 mg (n=1039)	Placebo (n=1046)
Median (range) age, y	45.0 (18.0–86.0)	470 (18.0–88.0)
Male	520 (50.0)	506 (48.4)
Race, n (%)		
White	738 (71.0)	749 (71.6)
Black or African American	50 (4.8)	44 (4.2)
Asian	146 (14.1)	149 (14.2)
American Indian or Alaska Native	95 (9.1)	93 (8.9)
Mean duration since first symptom, d (SD)	2.9 (1.1)	3.0 (1.1)
Number of risk factors for severe COVID-19, n (%)		
1	414 (39.8)	395 (37.8)
2	359 (34.6)	380 (36.3)
3	177 (17.0)	176 (16.8)
4	71 (6.8)	73 (7.0)
>4	16 (1.5)	22 (2.1)
SARS-CoV-2 serology (IgM, IgG) status, n (%)		
Negative	487 (46.9)	505 (48.3)
Positive	540 (52.0)	528 (50.5)

IgG=immunoglobulin G; IgM=immunoglobulin M; mITT1, modified intent-to-treat 1; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

- Symptoms present at baseline are shown in **Figure 1**.

Figure 1. Cough, headache, and muscle or body aches were the most common symptoms at baseline, with headache and muscle or body aches being the most common severe symptoms*

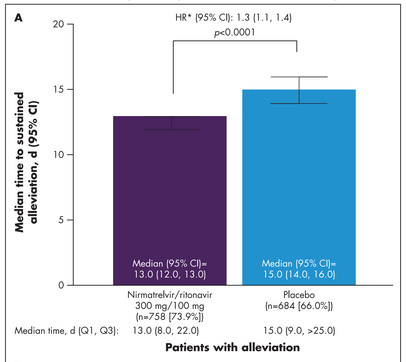


*Symptoms ordered as in Figure 3A.

RESULTS (continued)

- A greater number of patients achieved sustained alleviation and sustained resolution with nirmatrelvir/ritonavir 300 mg/100 mg compared with placebo.
  - A shorter median time to sustained alleviation was observed with nirmatrelvir/ritonavir 300 mg/100 mg (13 days) compared with placebo (15 days; $p<0.0001$; **Figure 2A**).
  - Similarly, a shorter median time to sustained resolution was observed with nirmatrelvir/ritonavir 300 mg/100 mg (16 days) vs placebo (19 days; $p=0.0008$; **Figure 2B**).

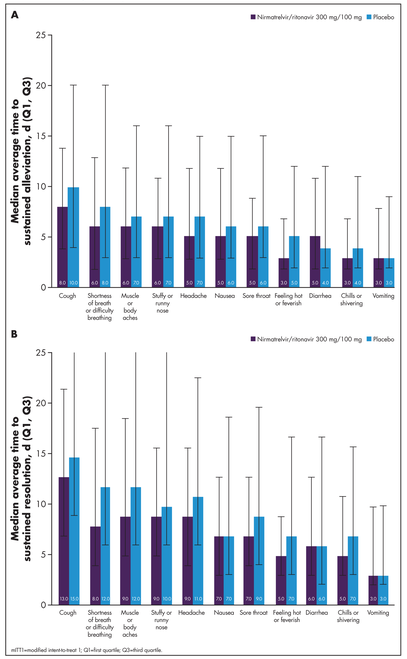
Figure 2 Nirmatrelvir/ritonavir treatment resulted in a (A) 2-day improvement in time to symptom alleviation vs placebo ($p<0.0001$) and (B) 3-day improvement in time to symptom resolution vs placebo ($p=0.0008$) in the mITT1 analysis set



*HR for nirmatrelvir/ritonavir treatment vs placebo.
HR=hazard ratio; mITT1, modified intent-to-treat 1; Q1=first quartile, Q3=third quartile.

- The median times to sustained alleviation and resolution were shorter for nirmatrelvir/ritonavir compared with placebo for most individual signs and symptoms.
  - Nonsevere cough, feeling hot or feverish, headache, and shortness of breath or difficulty breathing symptoms showed shorter times to both sustained alleviation and resolution in patients treated with nirmatrelvir/ritonavir compared with placebo (**Figure 3**).
  - The median time to sustained alleviation and sustained resolution of both cough and headache was 2 days less with nirmatrelvir/ritonavir 300 mg/100 mg compared with placebo (**Figure 3**).
  - The median times to sustained resolution of muscle or body aches and shortness of breath or difficulty breathing were 3 days and 4 days less, respectively, with nirmatrelvir/ritonavir (**Figure 3B**).
  - In both nirmatrelvir/ritonavir and placebo groups, vomiting, feeling hot/feverish, and chills/shivering were alleviated faster than other targeted signs/symptoms, whereas cough, shortness of breath or difficulty breathing, and muscle or body aches lasted longer (**Figure 3A**).

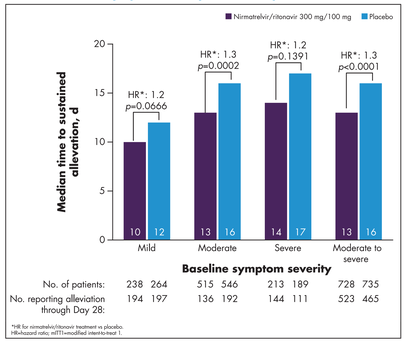
Figure 3. Nirmatrelvir/ritonavir treatment resulted in faster (A) alleviation and (B) resolution of all individual symptoms vs placebo with the exception of GI-related symptoms (mITT1 analysis set)



mITT1=modified intent-to-treat 1; Q1=first quartile; Q3=third quartile.

- The median times to sustained alleviation were shorter for nirmatrelvir/ritonavir compared with placebo regardless of baseline severity (**Figure 4**).
  - Among the patients who had moderate to severe symptoms at baseline (nirmatrelvir/ritonavir, n=728; placebo, n=735), the median time to sustained alleviation was significantly shorter with nirmatrelvir/ritonavir (13 days) vs placebo (16 days; $p<0.0001$).

Figure 4. Patients treated with nirmaltrelvir/ritonavir achieved sustained alleviation of COVID-19 symptoms regardless of baseline symptom severity (mITT1 analysis set)

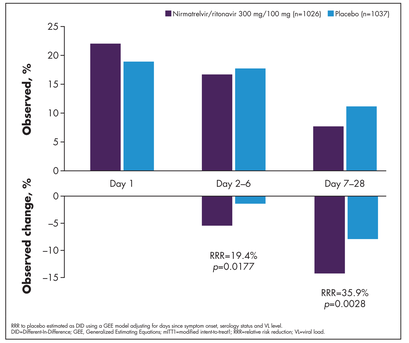


No. of patients:	238	264	515	546	213	189	728	735
No. reporting alleviation through Day 28:	194	197	136	192	144	111	523	465

*HR for nirmatrelvir/ritonavir treatment vs placebo.
HR=hazard ratio; mITT1=modified intent-to-treat 1.

- The proportion of patients with severe signs/symptoms in the nirmatrelvir/ritonavir compared with placebo group was substantially higher at baseline but significantly lower after treatment and during the follow-up period (Day 7 to Day 28), indicating that nirmatrelvir/ritonavir 300 mg/100 mg significantly reduced symptom severity through Day 28 (**Figure 5**).

Figure 5. Treatment with nirmatrelvir/ritonavir significantly reduced the percentage of patients with severe signs or symptoms from Days 2–6 and Days 7–28 relative to placebo (mITT1 analysis set)



RRR to placebo estimated as DID using a GEE model adjusting for days since symptom onset, serology status and VL level.
DID=Different-In-Difference; GEE, Generalized Estimating Equations; mITT1=modified intent-to-treat1; RRR=relative risk reduction; VL=viral load.

CONCLUSIONS

- **Nirmatrelvir/ritonavir 300 mg/100 mg treatment reduced duration of COVID-19 symptoms compared with placebo in adult patients at high risk of progressing to severe disease, shortening the time to symptom alleviation and resolution by 2–3 days.**
- **Nirmatrelvir/ritonavir 300 mg/100 mg treatment significantly reduced severe COVID-19 symptoms relative to placebo.**

REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available at: https://covid19.who.int/. Accessed September 19, 2022.
2. Docherty AB, et al. *BMJ.* 2020;369:m1985.
3. Kim L, et al. *Clin Infect Dis.* 2021;72(9):e206-e214.
4. US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for PAXLOVID™. Available at: https://labeling.pfizer.com/ShowLabeling.aspx?id=16474. Accessed June 30, 2022.
5. Hammond J, et al. *N Engl J Med.* 2022;386(15):1397-1408.
6. US Food and Drug Administration. Assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID-19 prevention or treatment. Guidance for Industry, October 16, 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs. Accessed October 3, 2022.

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DISCLOSURES

Jennifer Hammond, Heidi Leister-Tebbe, Annie Gardner, Paula Abreu, Weihang Bao, Wayne Wisemandle, Wajeeha Ansari, Magdalena Alicja Harrington, Rienk Pypstra, and James M. Rusnak are employees of Pfizer Inc and may hold stock or stock options. Kara W. Chew reports research grant funding to the institution from Merck Sharp & Dohme and has consulted for Pardes Biosciences. Abraham Simón-Campos reports personal fees from AstraZeneca and Roche.

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