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Nirmatrelvir/Ritonavir Reduces Duration of COVID-19 Symptoms Across Subgroups of High-Risk Patients

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Nirmatrelvir/ritonavir treatment accelerated symptom recovery in high-risk adults with mild to moderate COVID-19, resulting in significant 2- and 3-day reductions in median times to sustained alleviation and resolution of all targeted COVID-19 symptoms, respectively, and resulting in 4- to 6-day reductions within key patient subgroups.

Background

- Nirmatrelvir/ritonavir (NMV/r, Pfizer Inc) is approved as an oral treatment for mild to moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 disease.[1]
- The pivotal phase 2/3 EPIC-HR study (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) demonstrated an 86% relative-risk reduction against COVID-19–related hospitalization or all-cause mortality through Day 28 in adults with mild to moderate COVID-19 at increased risk of progression to severe disease who were treated with NMV/r within 5 days of symptom onset.[1,2]
- In addition to preventing severe outcomes, such as hospitalization and death, accelerating COVID-19 symptom recovery is a key goal of the current National Institutes of Health therapeutic management guidelines.[3]
- Here, we report additional secondary symptom–based endpoints from the EPIC-HR study, including times to sustained alleviation and resolution of symptoms overall and across patient subgroups.

Methods

- EPIC-HR (NCT04960202) was a phase 2/3, double-blind, randomized, placebo-controlled study that evaluated NMV/r in symptomatic, unvaccinated, nonhospitalized patients with COVID-19 and ≥1 risk factor for progression to severe disease.
- Eligible adults ≥18 years of age with confirmed SARS-CoV-2 infection and ≤5 days since symptom onset were randomized 1:1 to receive NMV/r 300 mg/100 mg or placebo orally every 12 hours for 5 days (10 doses total).
- The presence and severity (on 3- or 4-point scales) of 11 targeted symptoms attributed to COVID-19 (muscle or body aches, shortness of breath, chills, cough, diarrhea, fever, headache, nausea, stuffy or runny nose, sore throat, and vomiting), prespecified per US Food and Drug Administration guidelines,[4] were recorded by patients daily from Day 1 (pre-dose) through Day 28.
- Endpoints were assessed in the mITT1 population, defined as all patients who were assigned to study intervention, received ≥1 dose of study intervention, had ≥1 postbaseline visit through Day 28, and had not received nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization.
- Sustained alleviation was defined as the event occurring on the first of 4 consecutive days when all targeted symptoms that were scored as moderate or severe at study entry were scored as mild or absent AND all targeted symptoms that were scored as mild or absent at study entry were scored as absent. Sustained resolution was defined as the event occurring on the first of 4 consecutive days when all targeted symptoms were scored as absent.
- Times to sustained alleviation and resolution of all targeted symptoms within patient subgroups were assessed and compared between treatment groups (NMV/r vs placebo) by Kaplan-Meier analysis and using a Cox proportional hazard regression model in which the estimate of the hazard ratio for treatment, its confidence interval, and its *P* value were assessed.
- For missing data from participants discontinuing due to an adverse event or lack of efficacy, a baseline-observation-carried-forward approach was used. The last-observation-carried-forward method was used for other missing data.

Results

- Among 2113 randomized patients, 1966 (NMV/r, n=977; placebo, n=989) were included in the analysis.
- Demographic and baseline clinical characteristics between the NMV/r and placebo groups were similar (**Table 1**).

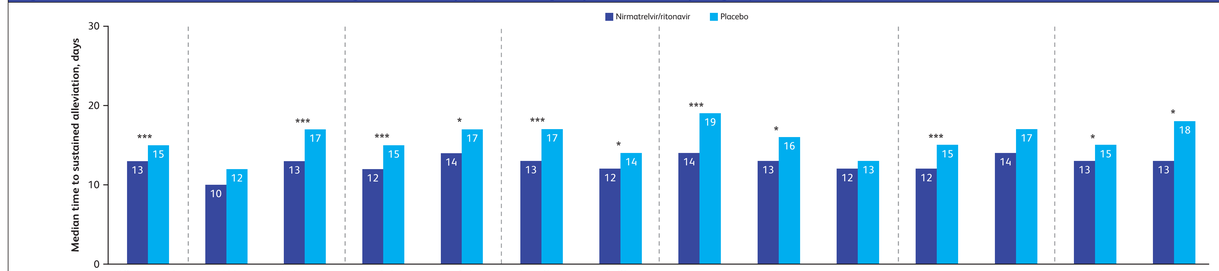
Table 1. Demographics and Baseline Characteristics (mITT1 Population)

Characteristic	Nirmatrelvir/ Ritonavir 300 mg/100 mg (n=977)	Placebo (n=989)
Age, median (range), y	44.0 (18.0–86.0)	46.0 (18.0–88.0)
Age group, y		
≤60	797 (81.6)	781 (79.0)
>60	173 (17.7)	205 (23.2)
Male sex	485 (49.6)	505 (51.1)
Race		
White	682 (69.8)	705 (71.3)
Asian	146 (14.9)	149 (15.1)
American Indian or Alaska Native	95 (9.7)	93 (9.4)
Black	44 (4.5)	31 (3.1)
BMI, mean (SD), kg/m^2	28.9 (5.4)	29.0 (5.5)
Time since first symptom, d		
≤3	671 (68.7)	647 (65.4)
>3	306 (31.3)	342 (34.6)
Mean (SD)	2.89 (1.1)	2.97 (1.1)
Viral RNA level, mean (SD), $\log_{10}$ copies/mL	4.7 (2.9)	4.7 (2.9)
Viral RNA level, $\log_{10}$ copies/mL		
0	171 (17.5)	166 (16.8)
<4	342 (35.0)	352 (35.6)
≥4	607 (62.1)	610 (61.7)
<7	676 (69.2)	706 (71.4)
≥7	273 (27.9)	256 (25.9)
Symptom severity*		
Mild	229 (24.9)	253 (26.5)
Moderate	483 (52.5)	515 (53.9)
Severe	202 (22.0)	181 (19.0)
Moderate to severe	685 (74.5)	696 (72.9)
SARS-CoV-2 serology, IgM and IgG status		
Negative	475 (48.6)	497 (50.3)
Positive	490 (50.2)	479 (48.4)

All data are n (%) unless otherwise stated.
BMI=body mass index; IgG=immunoglobulin G; IgM=immunoglobulin M; mITT1=modified intent-to-treat 1; NMV/r=nirmatrelvir/ritonavir.
*N for this category is 920 for the NMV/r 300-mg/100-mg group and 955 for the placebo group.

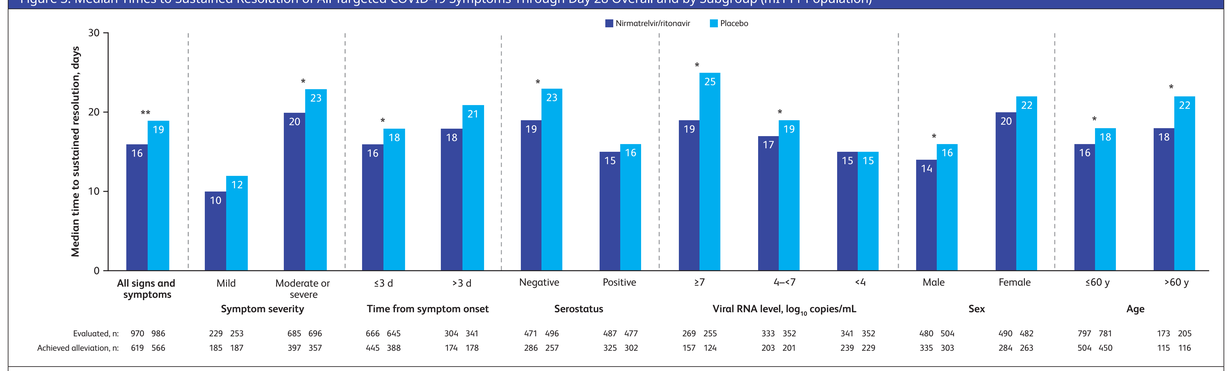
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Figure 2. Median Times to Sustained Alleviation of All Targeted COVID-19 Symptoms Through Day 28 Overall and by Subgroup (mITT1 Population)



mITT1=modified intent-to-treat 1; negative=absence of SARS-CoV-2 antibodies; NMV/r=nirmatrelvir/ritonavir; positive=presence of SARS-CoV-2 antibodies.
Significant differences between NMV/r and placebo groups are denoted with asterisks: *P≤0.05, **P≤0.001, and ***P≤0.0001.
Analysis of treatment effect within each subgroup on times to sustained alleviation was determined with a Cox proportional hazard model with independent variables of treatment and geographic region and with baseline SARS-CoV-2 serology status and baseline viral RNA level (<4 vs ≥4 $\log_{10}$ copies/mL) and baseline symptom onset duration (time from symptom onset, ≤3 vs >3 days) as covariates.

Figure 3. Median Times to Sustained Resolution of All Targeted COVID-19 Symptoms Through Day 28 Overall and by Subgroup (mITT1 Population)

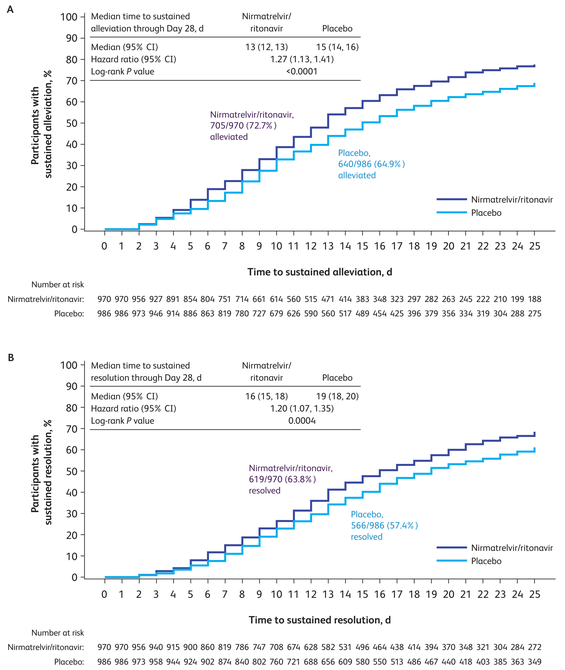


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Results (continued)

- NMV/r significantly reduced the median times to sustained alleviation and resolution of all targeted symptoms through Day 28: a 2-day reduction (13 vs 15 days; *P*<0.0001) in sustained alleviation and a 3-day reduction (16 vs 19 days; *P*=0.0004) in sustained resolution was observed relative to placebo (**Figure 1**).

Figure 1. Kaplan-Meier Analysis of Time to Sustained Alleviation (A) and Resolution (B) of All Targeted COVID-19 Symptoms Through Day 28 in the mITT1 Population



mITT1=modified intent-to-treat 1.

- Reduction in median times to sustained alleviation and resolution of all targeted symptoms was observed in patients treated with NMV/r vs those receiving placebo in all subgroups: by baseline symptom severity, time since symptom onset, baseline serostatus, viral RNA level, sex, and age (**Figure 2** and **Figure 3**).
  - NMV/r reduced median time to sustained alleviation in each of the patient subgroups examined. The largest reductions in median time to sustained alleviation included a 5-day median improvement among patients with baseline viral RNA level ≥7 $\log_{10}$ copies/mL (14 vs 19 days; *P*<0.0001) and patients >60 years of age (13 vs 18 days, *P*=0.0024); a 4-day improvement was observed among patients with moderate to severe symptoms at baseline (13 vs 17 days; *P*=0.0001) and patients who were seronegative (13 vs 17 days; *P*=0.0001; **Figure 2**).
  - Similarly, the largest reductions in median time to sustained resolution included a 6-day median improvement among patients with baseline viral RNA level ≥7 $\log_{10}$ copies/mL (19 vs 25 days; *P*=0.0272), a 4-day median improvement among patients >60 years of age (18 vs 22 days, *P*=0.0386), and a 4-day median improvement among patients who were seronegative (19 vs 23 days, *P*=0.0086; **Figure 3**).

Conclusions

- NMV/r significantly reduced the duration of COVID-19 symptoms compared with placebo through Day 28, shortening the median times to sustained alleviation and resolution of all targeted symptoms by 2 and 3 days, respectively, in high-risk patients with mild to moderate COVID-19.
- Treatment benefit of NMV/r in accelerating symptom recovery was observed consistently across patient subgroups (baseline symptom severity, time since symptom onset, serostatus, viral RNA level, sex, and age) with 4- to 6-day improvements in median times to sustained alleviation and resolution across key subgroups.
- Findings indicate that treatment with NMV/r may reduce COVID-19 burden in high-risk patients by reducing the duration of symptoms, allowing faster clinical recovery.
- These results are consistent with overall results from EPIC-HR (in which NMV/r significantly reduced COVID-19–related hospitalization and all-cause death compared with placebo)[1,2] and further demonstrate the added clinical benefit of NMV/r in accelerating symptom recovery among high-risk patients with mild to moderate COVID-19.

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