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Alleviation of COVID-19 Symptoms and Reduction in Healthcare Utilization Among High-risk Patients Treated With Nirmatrelvir/Ritonavir (NMV/R): A Phase 3 Randomized Trial

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Background. Nirmatrelvir/ritonavir (NMV/r) is an oral antiviral treatment for mild to moderate coronavirus disease 2019 (COVID-19).

Methods. This phase 2/3, double-blind, randomized (1:1) study assessed oral NMV/r 300 mg/100 mg versus placebo every 12 hours for 5 days in high-risk, unvaccinated, nonhospitalized, symptomatic adults with COVID-19 from 343 sites across 21 countries. In testing the primary endpoint of COVID-19–related hospitalization and all-cause deaths and key secondary endpoints, including symptom duration and COVID-19–related medical visits, type I error was controlled with prespecified sequential testing and the Hochberg procedure.

Results. Among 2113 randomized patients enrolled from July 2021 through December 2021, 1966 (NMV/r, n = 977; placebo, n = 989) were included in the prespecified analysis population (symptom onset ≤5 days, did not receive monoclonal antibodies). NMV/r significantly reduced times to sustained alleviation (median, 13 vs 15 days; hazard ratio = 1.27, $P < .0001$) and resolution (16 vs 19 days; hazard ratio = 1.20, $P = .0022$) through day 28 and significantly reduced the number of COVID-19–related medical visits and the proportion of patients with such visits. Hospitalized patients treated with NMV/r had shorter stays, none required intensive care unit admission or mechanical ventilation, and all were discharged to home/self-care. Fewer NMV/r-treated patients required additional treatment for COVID-19. No NMV/r-treated patients died through week 24 compared with 15 placebo-treated patients.

Conclusions. In addition to reducing COVID-19–related hospitalization or death from any cause through day 28, NMV/r was found to also reduce duration of COVID-19 symptoms and utilization of healthcare resources versus placebo in patients at high risk of progressing to severe disease.

Clinical Trial Information. ClinicalTrials.gov, NCT04960202, https://clinicaltrials.gov/study/NCT04960202

Keywords. COVID-19 drug therapy; symptoms; nirmatrelvir; ritonavir; EPIC-HR.

More than 775 million cumulative cases and 7.0 million deaths from coronavirus disease 2019 (COVID-19) have been reported globally [1]. The US Centers for Disease Control and Prevention estimated ≥97% of adults have antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through vaccination, infection, or both [2]. Despite this, severe illness from infection remains a serious public health threat [3]. Nirmatrelvir/ritonavir (NMV/r) is the first and only US Food and Drug Administration–approved oral treatment for mild to moderate COVID-19 in adults at high risk of progression to severe disease, and reduces hospitalization and death from COVID-19 [4, 5].

Severe cases of COVID-19 are associated with hospitalization, intensive care unit (ICU) admission, invasive mechanical ventilation, and death [6, 7]. During the pandemic years, COVID-19–related healthcare resource strains, such as limitations in

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emergency department, hospital, and ICU space, negatively affected healthcare and public health infrastructures [8, 9]. Patients with less severe disease may experience COVID-19 symptoms that interfere with daily functioning and activities. In addition to the key goal of preventing progression to severe disease, accelerating symptom recovery is a potential therapeutic goal as described in the National Institutes of Health therapeutic management guidelines for nonhospitalized patients [10]; this is a particularly relevant efficacy outcome for patients given the declining rate of severe COVID-19.

Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) was a phase 2/3 study that assessed NMV/r in nonhospitalized adults with mild to moderate COVID-19 at increased risk of progression to severe disease [11]. Data from EPIC-HR showed NMV/r was safe and effective, with an 89% and 88% relative risk reduction (RRR) against COVID-19–related hospitalization or all-cause mortality through day 28 when treatment was initiated within 3 or 5 days of symptom onset, respectively [11]. Final study results of the primary endpoint, which include data collected through week 24, and subgroup analyses are also reported. Here, we report additional efficacy endpoints from EPIC-HR, including key secondary and other supportive endpoints (eg, time to sustained alleviation and resolution of COVID-19 symptoms) from the prespecified sequential hypothesis testing.

METHODS

Study Design and Patients

Study design and enrollment criteria have previously been described in detail [11]. Briefly, this phase 2/3, double-blind, randomized, placebo-controlled trial recruited patients from July 2021 through December 2021 from 343 investigational sites across 21 countries (see Supplementary Appendix). Patients aged ≥18 years were eligible to participate if they had confirmed SARS-CoV-2 infection from a specimen collected within 5 days before randomization, onset of COVID-19–associated symptoms (see Supplementary Appendix) within 5 days before randomization with ≥1 symptom present on the day of randomization, ≥1 characteristic or coexisting condition associated with increased risk of developing severe COVID-19, and had not received a SARS-CoV-2 vaccine. Eligible patients were randomized 1:1 to receive NMV/r 300 mg/100 mg or placebo every 12 hours for 5 days. The Supplementary Appendix provides additional inclusion and exclusion criteria and information on prohibited prior or concomitant therapies, trial blinding, and randomization and blinding.

Ethical Conduct

As previously reported [11], all patients or their legally authorized representative provided written informed consent. The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. The protocol and related documents were approved by an institutional review board or ethics committee before study commencement.

Efficacy Endpoints

Table 1 shows the key secondary efficacy endpoints, including times to sustained alleviation and resolution of all targeted symptoms, proportion of patients with COVID-19–related medical visits, and proportion of patients with a resting peripheral oxygen saturation ≥95% at day 5 relative to day 1. For symptom-related endpoints, patients logged the presence and severity (on 3- or 4-point scales) of each of 11 prespecified targeted symptoms attributed to COVID-19 (see Supplementary Appendix) daily from day 1 (predose) through day 28 using an electronic handheld device.

Sustained alleviation was defined as 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 occurring on the first of 4 consecutive days when all targeted symptoms were scored as absent. COVID-19–related medical visits were collected through day 34 and categorized as hospitalization, emergency department, urgent care, practitioner's office, and other visits. Additional details of hospitalization, including length of stay, ICU admission, use of mechanical ventilation, and residence on discharge, as well as use of postentry treatments for COVID-19 (including supplemental oxygen and COVID-19–directed medications) and week 24 mortality, were collected.

Statistical Analysis

The procedures to control for type I error while testing for statistical significance were prespecified in the statistical analysis plan. Following the sequential testing procedure, all secondary endpoints were tested after statistical significance was achieved in the analyses of both the primary and first key secondary efficacy endpoints. The Hochberg procedure was used to further control for multiplicity [12]. Unadjusted *P* values were provided in all analyses and assessment of statistical significance was based on prespecified hierarchy of hypothesis testing.

Treatment effect (presented as hazard ratio [HR]) on times to sustained alleviation and resolution of all targeted symptoms through day 28 was assessed using a Cox proportional hazard model adjusting for geographic region, SARS-CoV-2 serology status (positive vs negative), baseline viral load (VL; <4 vs ≥4 $\log_{10}$ copies/mL), and days since symptom onset to start of treatment (≤3 vs >3 days). The median time to sustained alleviation or resolution was estimated using the Kaplan-Meier

Table 1. Results by Hierarchy of Hypothesis Testing

Endpoint	NMV/r	Placebo	Test Statistic	*P* Value, Inference
Primary efficacy endpoint				
Proportion of patients with COVID-19–related hospitalization or death from any cause through day 28 (mITT population[a]), %	0.752	6.888	δ = –6.137% RRR = 89.1%	<.0001, S (primary)
Key secondary efficacy endpoints				
Proportion of patients with COVID-19–related hospitalization or death from any cause through day 28 (mITT1 population[b]), %	0.933	6.571	δ = –5.638% RRR = 85.8%	<.0001, S (1st sequential)
Time to sustained alleviation of all targeted signs/symptoms through day 28 (mITT1 population), d	Median = 13	Median = 15	HR = 1.266	<.0001, S (2nd sequential)
Other secondary efficacy endpoints				
Time to sustained resolution of all targeted signs/symptoms through day 28 (mITT1 population), d	Median = 16	Median = 19	HR = 1.200	.0022, S (Hochberg)
Number of COVID-19-related medical visits (mITT1 population)	Mean = 0.041	Mean = 0.129	δ (LS mean ratio) = 0.357	<.0001, S (Hochberg)
Proportion of patients with a resting peripheral oxygen saturation ≥95% at days 1 and 5 (mITT1 population), %	Day 1 = 93.3 Day 5 = 91.6	Day 1 = 92.2 Day 5 = 87.6	OR (NMV/r) = 20.9 OR (placebo) = 12.5	.2810, NS (Hochberg)

Abbreviations: δ, difference of proportions; LS, least squares; HR, hazard ratio; mITT, modified intent-to-treat; mITT1, modified intent-to-treat 1; NS, not significant; NMV/r, nirmatrelvir/ritonavir; OR, odds ratio; RRR, relative risk reduction; S, significant.

[a]The mITT population (NMV/r, n = 671; placebo, n = 647) includes all patients randomly assigned to a study intervention who received ≥1 dose of the study intervention, had ≥1 postbaseline visit through day 28, had not received nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment at baseline, and were treated within 3 d after COVID-19 symptom onset.

[b]mITT1 population (NMV/r, n = 977; placebo, n = 989) includes all patients randomly assigned to a study intervention who received ≥1 dose of the study intervention, had ≥1 postbaseline visit through day 28, at baseline had not received nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated within 5 d after COVID-19 symptom onset.

method. Sustained alleviation or resolution required 4 consecutive days of observed (not missing) symptom diary data and was not achieved if patients were hospitalized for COVID-19 treatment or died from any cause through day 28. A sensitivity analysis was performed that did not consider all patients who had COVID-19–related hospitalization or all-cause death as not achieving alleviation or resolution.

The number of COVID-19–related medical visits was assessed using a negative binomial regression model with the log-number of days of data collection as the offset variable. As a supportive analysis, a Fisher exact test was used to compare the proportion of patients with such visits. The effect of baseline resting peripheral oxygen saturation level (≥95% vs <95%) on the oxygen saturation level at day 5 was calculated as an odds ratio, which was then compared between treatment groups with a Breslow-Day test for homogeneity in the odds ratios. The homogeneity or lack thereof was further examined by assessing treatment effect in subgroups of patients defined by baseline oxygen saturation level. Supportive descriptive statistics were provided for healthcare utilization parameters including ICU status, need for oxygen support, mechanical ventilation, and postentry use of COVID-19–directed medications. Because most participants were not hospitalized and spent no time in the hospital, the bootstrap method was used to compare the average number of days in the hospital between treatment groups.

RESULTS

Patients

Of 2246 patients randomized in EPIC-HR recruited from July 2021 through December 2021 [11], 1966 patients (NMV/r, n = 977; placebo, n = 989) were treated within 5 days of symptom onset, did not receive or were not expected to receive monoclonal antibodies for COVID-19 at the baseline visit, and were included in the analysis population (Figure 1). Demographic and baseline clinical characteristics were similar in the 2 groups (Supplementary Table 2). COVID-19 symptoms present at baseline were generally balanced between the groups (Supplementary Figure 2), with cough, muscle or body aches, and headache being the most common. More patients treated with NMV/r reported at least 1 severe symptom at baseline versus placebo (22.0% vs 19.0%).

COVID-19–related Hospitalization and All-cause Death and Safety

Final study results of the primary endpoint, COVID-19–related hospitalization and all-cause death, which include data collected through week 24, and subgroup analyses are reported in Supplementary Figure 1, and safety is reported in Supplementary Table 1. Efficacy and safety results were generally consistent with the originally reported data [11].

Alleviation and Resolution of COVID-19 Symptoms

Patients receiving NMV/r were 26.6% more likely to achieve sustained symptom alleviation (HR, 1.27; 95% confidence interval [CI]: 1.13–1.41; $P < .0001$) and 20.0% more likely to achieve sustained symptom resolution by day 28 (HR, 1.20; 95% CI: 1.07–1.35; $P = .0022$). There was a significant 2-day reduction (13 vs 15 days) in median time to sustained symptom alleviation versus placebo ($P < .0001$; Figure 2*A*) and a 3-day reduction (16 vs 19 days) in median time to sustained symptom resolution versus placebo ($P = .0004$; Figure 2*B*). The treatment benefit in times to sustained alleviation and resolution remained statistically significant with or without accounting for

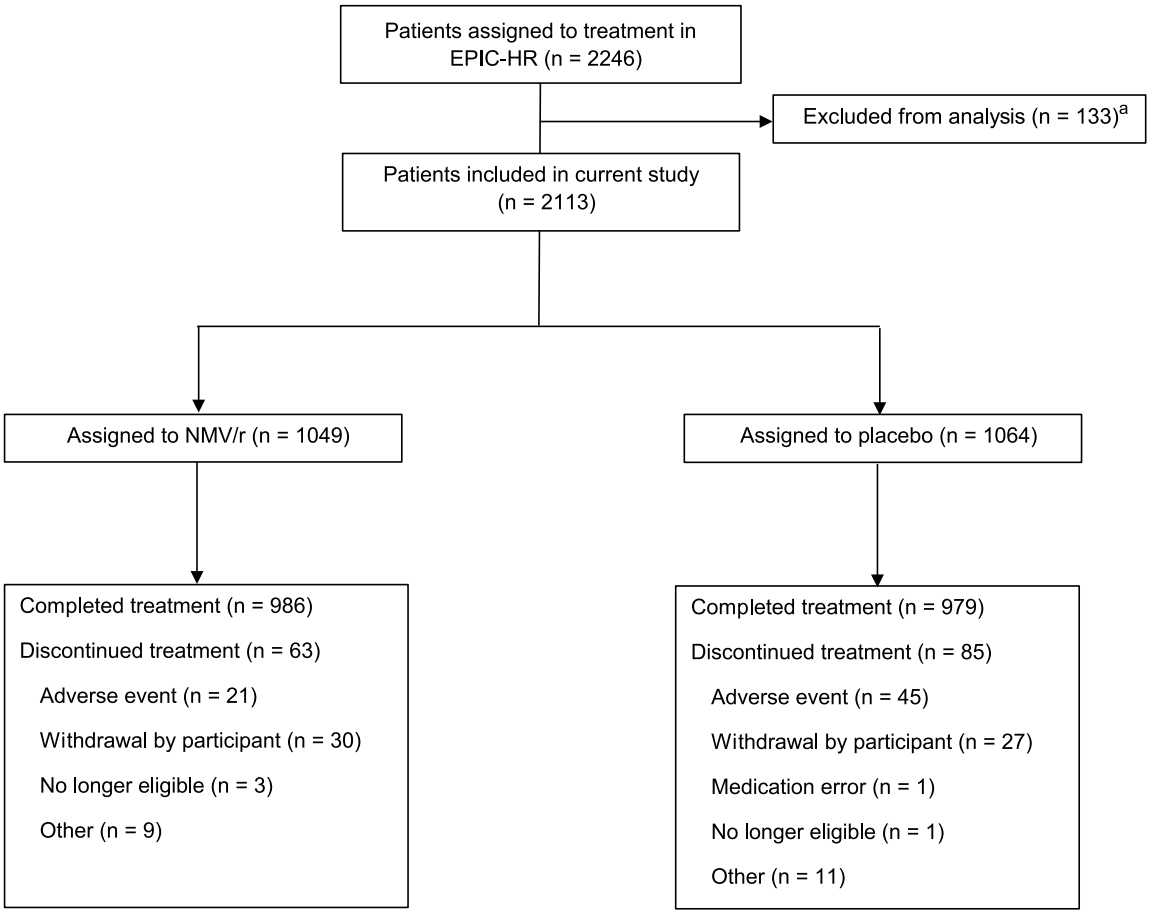

Figure 1. CONSORT diagram detailing enrollment and randomization. [a]Data for patients were excluded from 2 sites (n = 133) from the full analysis set: 1 site because of identified GCP noncompliance and 1 site because of unusual patterns in viral RNA concentration and sequencing data (see Supplementary Appendix, Sensitivity Analyses; Supplementary Table 6). GCP, good clinical practice; NMV/r, nirmatrelvir/ritonavir.

COVID-19–related hospitalizations or all-cause deaths (Supplementary Figures 3*A, B*).

When assessing individual symptoms, NMV/r shortened the median times to sustained alleviation and resolution by 1 to 2 days and 1 to 3 days, respectively, for each symptom, except for gastrointestinal-related symptoms. In both groups, vomiting, feeling hot or feverish, and chills or shivering were alleviated faster than other targeted symptoms, whereas cough, shortness of breath or difficulty breathing, and muscle or body aches lasted longer. The largest treatment benefit (3-day reduction) was observed in median time to sustained resolution of shortness of breath or difficulty breathing and muscle or body aches. The presence and severity of individual targeted COVID-19 symptoms over time through day 28 is shown in Supplementary Table 3.

Treatment with NMV/r reduced the median time to sustained alleviation in all subgroups by baseline symptom severity, serostatus, VL time since symptom onset, age, and sex. The reduction was more apparent among patients with moderate or severe symptoms at baseline (13 vs 17 days; $P = .0001$), seronegative patients (13 vs 17 days; $P = .0001$), patients with baseline VL ≥ 7 $\log_{10}$ copies/mL (14 vs 19 days; $P < .0001$), and patients aged >60 years (13 vs 18 days; $P = .0011$; Supplementary Figure 4*A*). The reduction in median time to sustained symptom resolution was more apparent in the same patient subgroups: patients with moderate or severe symptoms at baseline (20 vs 23 days; $P = .010$), seronegative patients (19 vs 23 days; $P = .0086$), patients with baseline VL ≥ 7 $\log_{10}$ copies/mL (19 vs 25 days; $P = .027$), and patients aged >60 years (18 vs 22 days; $P = .022$; Supplementary Figure 4*B*).

Healthcare Utilization

COVID-19–related medical visits occurred at a significantly lower rate in the NMV/r group than in the placebo group (64.3% rate reduction; $P < .0001$). Through day 34, 2.3% of patients in the NMV/r group (22/977) and 8.4% of patients in the placebo group (83/989) reported any COVID-19–related medical visit, corresponding to a 73.2% RRR with treatment ($P < .0001$; Figure 3). These observations were consistent

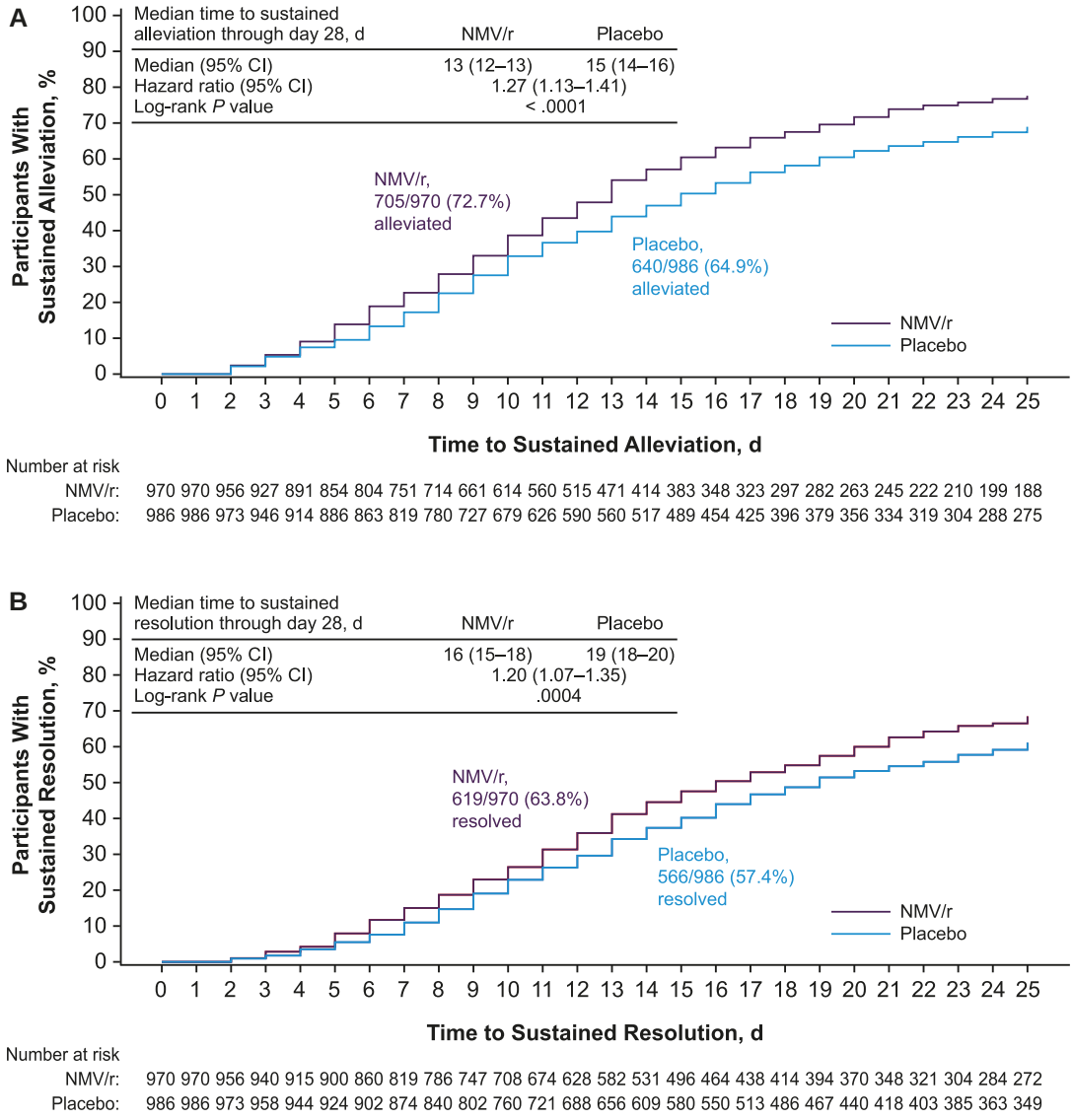

Figure 2. Times to sustained (*A*) alleviation and (*B*) resolution of all targeted COVID-19 symptoms through day 28 (mITT1 population). mITT1, modified intent-to-treat 1; NMV/r, nirmatrelvir/ritonavir.

across all predefined types of medical visits, including hospitalization and visits to the emergency department, practitioner's office, urgent care, and other visits. The percentage of patients with any COVID-19–related medical visit was lower in the NMV/r arm compared with placebo regardless of the severity of COVID-19 symptoms at baseline, with the absolute difference in percentage of patients with events greatest in patients with severe symptoms (Supplementary Table 4).

Nine patients treated with NMV/r (0.9%) and 63 patients treated with placebo (6.4%) were hospitalized for treatment of COVID-19 through day 28 (RRR, 85.5%; $P < .0001$). Among those hospitalized, no patients (0/9, 0%) in the NMV/r group were admitted to the ICU or required mechanical ventilation, compared with 9 of 63 (14.3%) and 4 of 63 (6.3%), respectively, in the placebo group (Figure 3). On average, participants in the NMV/r group spent 8.7 days in the hospital per 100 patients compared with 76.6 in the placebo group. NMV/r reduced the average number of days in the hospital by 88.6%, or 67.9 days per 100 patients, during the study ($P < .0001$). All patients in the NMV/r arm with a known discharge status were discharged to home self-care. Among patients in the placebo group, 54.7% were discharged to home self-care; others died in the hospital, were discharged to home and required assistance of home healthcare/family/friends, or were transferred to a nursing or rehabilitation facility. Through week 24, there were no deaths among patients treated with NMV/r compared with 15 deaths among placebo recipients: 14 were related to COVID-19, 3 deaths were

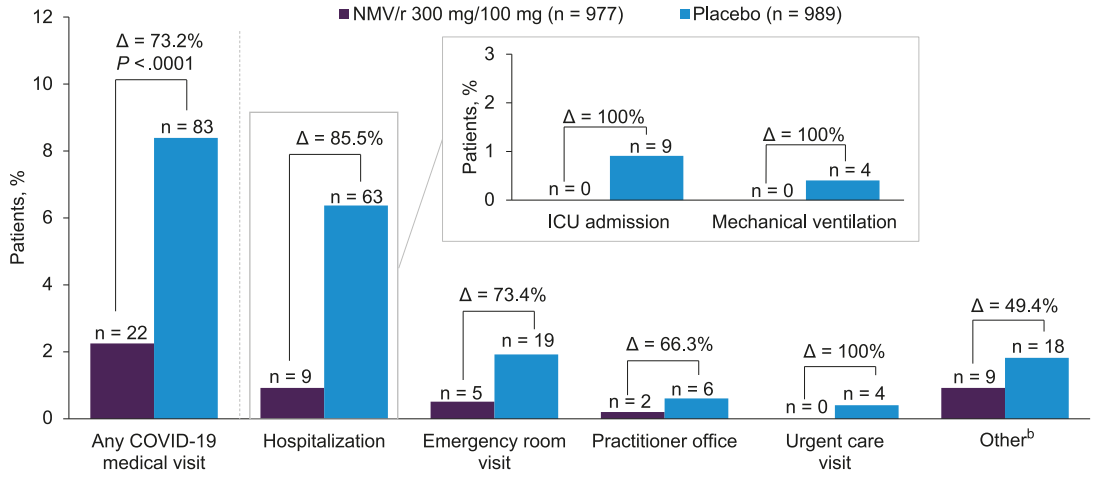

Figure 3. COVID-19–related medical visits and deaths due to any cause[a] (mITT1 population). [a]COVID-19–related hospitalizations were assessed through day 28, whereas other categories of COVID-19 medical visits were reported through day 34 visit. [b]Other includes use of home healthcare services, telephone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

reported after day 28, and 1 (on day 96) was due to sepsis associated with relapsed acute myeloid leukemia.

The overall test of proportion of patients with a resting peripheral oxygen saturation ≥95% at day 5 relative to day 1 was not significant (Table 1). However, NMV/r reduced the risk of patients having oxygen saturation <95% at day 5 by 12.1% ($P = .61$) and 49.7% ($P = .014$) in patients with baseline oxygen saturation <95% and ≥95%, respectively (Supplementary Table 5). A larger treatment benefit was observed when patients who were hospitalized for COVID-19 or died were assumed to have day 5 resting peripheral oxygen <95%; nirmatrelvir/ritonavir reduced the risk by 14.7% ($P = .49$) and 63.3% ($P < .0001$) in patients with baseline oxygen saturation <95% and ≥95%, respectively. Consistent with the oxygen saturation findings, fewer patients in the NMV/r group required supplemental oxygen support for COVID-19 versus placebo (10/977 [1.0%] vs 52/989 [5.2%]; RRR, 80.6%).

Post-entry COVID-19–directed medications in either treatment group included monoclonal antibodies, hyperimmune plasma COVID-19, favipiravir, remdesivir, and systemic corticosteroids. A lower proportion of patients in the NMV/r group received these medications than in the placebo group: systemic corticosteroids (4.6% vs 9.3%), favipiravir (2.8% vs 3.4%), monoclonal antibodies (0.3% vs 0.6%), remdesivir (0.3% vs 1.6%), and hyperimmune plasma COVID-19 (0.1% vs 0.1%).

DISCUSSION

The EPIC-HR study showed that NMV/r 300 mg/100 mg met its primary endpoint, significantly reducing the risk of COVID-19–related hospitalization or all-cause mortality through day 28 in adult patients at high risk of progressing to severe disease, achieving an 89% RRR when treatment was initiated within 3 days of symptom onset [11]. Here, we reported additional benefits of NMV/r treatment in alleviating COVID-19 symptoms and reducing healthcare resource utilization. Statistical significance was achieved in all primary and secondary endpoints prespecified in the sequential testing and Hochberg procedure to control for type I error (Table 1), with the exception of resting peripheral oxygen saturation ≥95% at days 1 and 5, where a numerically nonsignificant trend in reduced frequency of postbaseline resting peripheral oxygen <95% was seen with NMV/r.

Treatment with NMV/r reduced the duration of COVID-19 symptoms compared with placebo through day 28, shortening the median times to sustained symptom alleviation and resolution of all targeted symptoms by 2 and 3 days, respectively. The impact of COVID-19–related hospitalization and deaths (primary events) on the times to sustained alleviation and resolution was assessed in this study. When establishing the treatment benefit in times to sustained symptom alleviation and resolution, patients with a primary event through day 28 were considered not to have achieved alleviation or resolution. Further analyses showed that the NMV/r treatment effect on symptom relief remained statistically significant ($P < .05$) when times to sustained symptom alleviation and resolution were assessed independent of hospitalization or death (Supplementary Figures 2*A*, *B*).

During its peak, the COVID-19 pandemic strained the health systems in many countries [13, 14]. Treatment with NMV/r significantly reduced the number of required COVID-19–related medical visits compared with placebo and resulted in other healthcare benefits including fewer hospitalizations with shorter durations, no need for mechanical

ventilation or ICU admissions, reduced need for oxygen support, and reduced use of COVID-19–directed medications. The importance of having effective COVID-19 treatments such as NMV/r to reduce burden on healthcare systems, both ambulatory and hospital based, should not be underestimated.

Patients in this study were recruited from July through December 2021 [11], when Delta was the predominant variant [15]. Although potential effects of new variants on the clinical efficacy of NMV/r were not evaluated in this study, the activity of NMV/r against new variants has been demonstrated in vitro and in vivo [16, 17]. Additionally, real-world data support the efficacy of NMV/r across SARS-CoV-2 variant types, with several studies showing NVM/r relative effectiveness ranging between 44% and 83% during the Omicron-predominant period [18–24].

A limitation of EPIC-HR is that enrollment was restricted to unvaccinated patients [11]. Although patients with previous confirmed infection were excluded, approximately 51% were seropositive at baseline [11]. Reductions in times to alleviation and resolution of COVID-19 symptoms were observed in the subgroup of seropositive patients, though not to the same extent as that observed in seronegative patients. In the current environment, where rates of preexisting immunity are high (either acquired naturally or through vaccination) [1, 25, 26] and the virus continues to evolve, caution may be needed when generalizing the results of this study to clinical practice that would likely include individuals with existing immunity, either through prior infection or vaccination. The phase 2/3 Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients trial (EPIC-SR; NCT05011513) enrolled unvaccinated adults at standard risk as well as vaccinated adults at high risk of progression to severe disease [16, 27–29]. Though the primary endpoint of reducing time to sustained alleviation of COVID-19 symptoms was not met, a 1-day improvement in median time to sustained alleviation was observed in patients treated with NMV/r and a clinically meaningful reduction in COVID-19–related hospitalizations and all-cause deaths was observed, including among fully vaccinated patients with risk factors for severe COVID-19 [29]. Further, data collected across multiple studies support the real-world effectiveness of NMV/r in the Omicron era and among vaccinated patients [18–24, 30]. Based on a population-based cohort study simulating a clinical trial, it was estimated that of 51.5 million COVID-19 cases in the United States between December 2021 and February 2023, approximately 48 000 deaths and 135 000 hospitalizations could have been prevented at 50% uptake of NMV/r [31]. Thus, the efficacy of NMV/r in the post-Delta era remains relevant.

In conclusion, results of this analysis add to previously published findings [11] showing NMV/r not only reduces the risk of hospitalization or death in symptomatic, high-risk adults with mild to moderate COVID-19 but also consistently demonstrated efficacy in alpha-protected secondary and supportive efficacy endpoints. These findings suggest that NMV/r treatment may reduce the COVID-19 burden in high-risk patients by (1) reducing the duration and severity of symptoms and (2) reducing the use of healthcare resources, particularly hospitalization and emergency room visits, which may reduce the burden of COVID-19 on healthcare systems during future waves of infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. H. and H. L. T. were involved in study design, data analysis, and data verification. A. G., W. A., K. W. C., R. P., and J. M. R. were involved in study design and data analysis. P. A., W. B., and W. W. were involved in study design, data analysis, data verification, and statistical analysis. M. A. H. was involved in study design. A. S. C. was involved in data analysis. All authors had access to the data and contributed to the writing of the manuscript.

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Data Availability Statement. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Potential conflicts of interest. J. H., H. L. T., A. G., P. A., W. B., W. W., W. A., M. A. H., R. P., and J. M. R. are employees of Pfizer and may hold stock or stock options. K. W. C. reports completed research grant funding to the institution from Merck Sharp & Dohme and has consulted for Pardes Biosciences. A. S. C. reports payments as a scientific advisor and speaker on behalf of Pfizer. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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