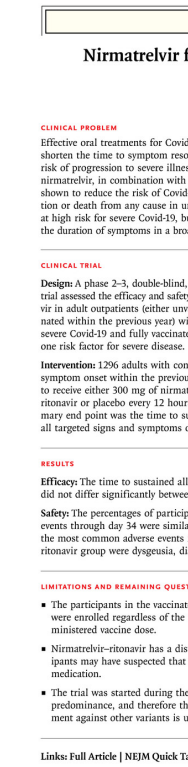
daily from day 1 through day 28. The primary end point was the time to sustained alleviatio
signs and symptoms. Covid-19–related hospitalization and death from any cause were also

RESULTS

Among the 1296 participants who underwent randomization and were included in the full analysis population, 1288 received at least one dose of nirmatrelvir–ritonavir (654 participants) or placebo (634 participants) and had at least one postbaseline visit. The median time to sustained alleviation of all targeted signs and symptoms of Covid-19 was 12 days in the nirmatrelvir–ritonavir group and 13 days in the placebo group (P=0.60). Five participants (0.8%) in the nirmatrelvir–ritonavir group and 10 (1.6%) in the placebo group were hospitalized for Covid-19 or died from any cause (difference, −0.8 percentage points; 95% confidence interval, −2.0 to 0.4). The percentages of participants with adverse events were similar in the two groups (25.8% with nirmatrelvir–ritonavir and 24.1% with placebo). In the nirmatrelvir–ritonavir group, the most commonly reported treatment-related adverse events were dysgeusia (in 5.8% of the participants) and diarrhea (in 2.1%).


Nirmatrelvir f

CLINICAL PROBLEM

Effective oral treatments for Covid
shorten the time to symptom reso
risk of progression to severe illnes
nirmatrelvir, in combination with
shown to reduce the risk of Covid
tion or death from any cause in u
at high risk for severe Covid-19, b
the duration of symptoms in a bro

CLINICAL TRIAL

Design: A phase 2–3, double-blind,
trial assessed the efficacy and safet
vir in adult outpatients (either unv
nated within the previous year) wi
severe Covid-19 and fully vaccinate
one risk factor for severe disease.

Intervention: 1296 adults with con
symptom onset within the previou
to receive either 300 mg of nirmat
ritonavir or placebo every 12 hour
mary end point was the time to su
all targeted signs and symptoms c

RESULTS

Efficacy: The time to sustained all
did not differ significantly betwee

Safety: The percentages of particip
events through day 34 were simila
the most common adverse events
ritonavir group were dysgeusia, di

LIMITATIONS AND REMAINING QUEST

- The participants in the vaccinat
were enrolled regardless of the
ministered vaccine dose.
- Nirmatrelvir–ritonavir has a dis
ipants may have suspected that
medication.
- The trial was started during the
predominance, and therefore th
ment against other variants is u

Links: Full Article | NEJM Quick Ta

Download a P

CONCLUSIONS

The time to sustained alleviation of all signs and symptoms of Covid-19 did not differ significantly between participants who received nirmatrelvir–ritonavir and those who received placebo. (Supported by Pfizer; EPIC-SR Clin NCT05011513.)

QUICK TAKE

Nirmatrelvir for Covid-19 Outpatients

2m 21s

The current phase 2–3 trial evaluated the efficacy and safety of nirmatrelvir–ritonavir in no
symptomatic Covid-19 who either were at standard risk for severe Covid-19 (i.e., without ris
either unvaccinated or without vaccination within the previous 12 months) or were fully vac
progression to severe Covid-19.

Methods

TRIAL DESIGN AND PARTICIPANTS

We conducted the Evaluation of Protease Inhibition for Covid-19 in Standard-Risk Patients
double-blind, randomized, placebo-controlled trial to assess the efficacy, safety, and side-e
ritonavir. Eligible participants were at least 18 years of age and had reverse-transcriptase–p
(RT-PCR)–confirmed or rapid antigen–confirmed SARS-CoV-2 infection and associated sig
(Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM
of symptoms occurring 5 or fewer days before randomization. Participants were required to
prespecified Covid-19 sign or symptom on the day of randomization and to be capable of pr
consent.

Patients with any predefined underlying condition associated with an increased risk of seve
participation if they had been fully vaccinated against Covid-19 (i.e., if they had received a c
authorized Covid-19 vaccine).[2-5] In addition, patients without underlying conditions associ
severe Covid-19 were eligible if they had not received a Covid-19 vaccine. After authorizatio
the Food and Drug Administration for the treatment of Covid-19 in patients with risk factor
December 2021, the trial protocol was amended to exclude all patients with risk factors for
clinical balance) and to allow enrollment of patients without underlying conditions associa
severe Covid-19 who had not received a Covid-19 vaccine within the previous 12 months. Ad
in the Supplementary Appendix and in the protocol (available at NEJM.org).

All participants provided written informed consent. The trial was conducted in accordance
derived from international guidelines (see the Supplementary Appendix) and local laws and
and other relevant documents were each approved by an institutional review board or ethic
initiation. Nirmatrelvir and matching placebo were manufactured by Pfizer, and ritonavir t
and tested by Hetero Labs. Blinding was performed by Pfizer by means of overencapsulatio

Pfizer was responsible for the trial design and conduct and for data collection, analysis, an
draft of the manuscript was written by medical writers (funded by Pfizer) under direction f
were available to the authors, who vouch for the accuracy and completeness of the data and
to the protocol.

TRIAL PROCEDURES

After a screening period that lasted no longer than 48 hours, participants were randomly as
use of an interactive response technology system to receive either nirmatrelvir–ritonavir (3
100 mg of ritonavir) or placebo (consisting of inactive filler ingredients) every 12 hours for

The prespecified key secondary end point was Covid-19–related hospitalization or death fr
Related secondary end points were the number of medical visits and the number of days in
unit (ICU) related to Covid-19 through day 28. Viral load was evaluated as described previou
assessed as at or above the lower limit of quantification or below the lower limit of quantifi
milliliter). Viral load rebound was then evaluated on day 10 or day 14 and was defined eithe
copies per milliliter or higher on day 10 or day 14 in a patient with a viral load that had beer
quantitation on day 5 or as a viral load increase by at least 0.5 $\log_{10}$ copies per milliliter fro
viral load of 3.0 $\log_{10}$ copies per milliliter or higher in a patient with a viral load that had be
of quantitation at day 5, day 10, or day 14. Symptom rebound was also evaluated and was de
symptoms (total symptom score increased by ≥4 points; scores range from 0 [no symptom
symptoms]) after any abatement of symptoms.

SAFETY

The secondary objective was to describe the safety and side-effect profile of nirmatrelvir–ri
placebo, with safety measured as the incidence of adverse events that emerged during the t
adverse events, and adverse events that led to discontinuation of nirmatrelvir–ritonavir or p
evaluated in the safety analysis population, which included all participants who received at
nirmatrelvir–ritonavir or placebo. The safety follow-up period lasted through day 34.

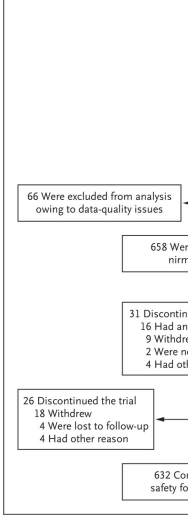
STATISTICAL ANALYSIS

Initially, we planned to enroll 1140 participants to ensure that 800 participants would be en
symptom onset, which would provide 90% power to detect a 25% difference in the time to
targeted Covid-19 signs and symptoms (8 days vs. 6 days), assuming that 18% of the partici
participation and that approximately 30% of the participants would undergo randomizatio
symptom onset. The protocol was later amended to include more participants to allow for
secondary efficacy end point (a composite of Covid-19–related hospitalization or death fro
days after enrollment).

The primary end point, the time to sustained alleviation of all Covid-19–related signs or sy
between the groups with the use of a log-rank test. The median time to sustained alleviatio
Kaplan–Meier method within each group. For the key secondary end point, the cumulative
who were hospitalized for Covid-19 or died during the first 28 days of the trial was estimate
of the Kaplan–Meier method and was compared between the groups with the use of the Wa
intervals, the corresponding estimate of the standard error was computed with Greenwood
Covid-19–related medical visits through day 28 was compared between the groups with a ne
model. The mean number of days spent in the hospital in each group was summarized and
bootstrap method with 100,000 replicates, with each replicate randomly selected (with rep
set.

The primary end point was tested at a significance level of 0.05. If the results of this test w
confidence intervals would be reported for secondary end points. These 95% confidence in

were women (54.0%), and the median age at enrollment was 42 years. Most participants were White (78.5%), and 41.4% identified as Hispanic or Latino; 48.6% had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 25 or higher at screening (mean, 26.3). All the participants had confirmed SARS-CoV-2 infection, and 72.5% underwent randomization within 3 days after symptom onset. Slightly more than half the participants (56.9%) had received previous Covid-19 vaccination (most commonly with mRNA vaccines), and 49.9% had at least one risk factor for severe Covid-19; the most common risk factor was cigarette smoking (in 13.3% of the participants), and the most common coexisting condition was hypertension (in 12.3%). Eleven participants who had at least one risk factor and were unvaccinated were not included in the subgroup analyses. Adherence (defined as having taken 80 to 115% of t tablets) was 94.8% in the nirmatrelvir–ritonavir group and 96.5% in the placebo group.



Enrollment an

EFFICACY

Among the 1288 participants who received at least one dose of nirmatrelvir–ritonavir or placebo and had at least one postbaseline visit, the median time to sustained alleviation of all targeted Covid-19 signs or symptoms through day 28 was 12 days in the nirmatrelvir–ritonavir group and 13 days in the placebo group, a difference that was not significant (P=0.60) (Table 2). Similar results were observed in the high-risk subgroup (i.e., participants who had been vaccinated and had at least one risk factor for severe illness) and in the standard-risk subgroup (i.e., those who had no risk factors for severe illness and had never been vaccinated or had not been vaccinated within the previous 12 months).

A key secondary end point in the trial was Covid-19–related hospitalization or death from any cause (see Table S4 for data pertaining to this end point, including subgroup analyses). A total of 5 of the 654 participants (0.8%) who received nirmatrelvir–ritonavir and 10 of the 634 (1.6%) who received placebo were hospitalized for Covid-19 or died from any cause through day 28, which corresponded to a difference of −0.8 percentage points (95% confidence interval [CI], −2.0 to 0.4). One high-risk vaccinated participant in the placebo group died. None of the 5 participants in the nirmatrelvir–ritonavir group who were hospitalized were admitted to the ICU, whereas 3 of 10 participants in the placebo group were admitted to the ICU. In a planned subgroup analysis involving high-risk participants, hospitalization or death occurred in 3 (0.9%) in the nirmaltrelvir–ritonavir group and 7 (2.2%) in the placebo group (difference, −1.3 percentage points; 95% CI, −3.3 to 0.7).

TABLE 1

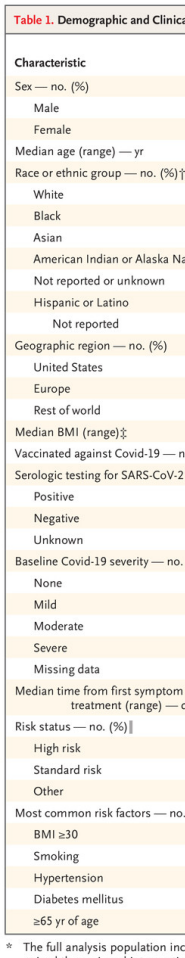


Table 1. Demographic and Clinica

Characteristic
Sex — no. (%)
Male
Female
Median age (range) — yr
Race or ethnic group — no. (%)†
White
Black
Asian
American Indian or Alaska Na
Not reported or unknown
Hispanic or Latino
Not reported
Geographic region — no. (%)
United States
Europe
Rest of world
Median BMI (range)‡
Vaccinated against Covid-19 — n
Serologic testing for SARS-CoV-2
Positive
Negative
Unknown
Baseline Covid-19 severity — no.
None
Mild
Moderate
Severe
Missing data
Median time from first symptom treatment (range) — d
Risk status — no. (%)‖
High risk
Standard risk
Other
Most common risk factors — no.
BMI ≥30
Smoking
Hypertension
Diabetes mellitus
≥65 yr of age

* The full analysis population inc
ceived the assigned interventio
issues. Percentages may not to
disease 2019, and SARS-CoV-2
† Race and ethnic group were rep
‡ Data were missing for 2 partici
§ Participants were considered to
cleocapsid antigen or the spike
¶ The most severe targeted sign
‖ High risk was defined by the pr
by the absence of such risk fact
nated or had not been vaccinat
** Risk factors occurring in at leas

Demographic
Participants Ir

group.

By day 14, viral load rebound had occurred in 4.3% of the participants in the nirmatrelvir–ritonavir group and 4.1% of those in the placebo group; symptom rebound occurred in 11.4% and 16.1%, respectively, and symptom and viral load rebound together occurred in 1.2% and 0.5%, respectively. Three p load rebound were hospitalized (one in the nirmatrelvir–ritonavir group and two in the pla consistent temporal relationship between viral load rebound and hospitalization.

Time to Susta Signs and Sym

SAFETY

Adverse events that emerged during the treatment period, serious adverse events, and adve discontinuation occurred in similar percentages of participants in the two groups (Table 3) participants with adverse events of any cause during the treatment period were 25.8% in th group and 24.1% in the placebo group and did not differ markedly between vaccinated and the nirmatrelvir–ritonavir group, 24 participants (3.7%) reported grade 3 or 4 adverse even events occurred; the corresponding values in the placebo group were 25 (3.9%) and 1 (0.2% were reported by 8 participants (1.2%) receiving nirmatrelvir–ritonavir and by 12 (1.9%) rec these events were considered by the investigator to be related to nirmatrelvir–ritonavir or p adverse events reported by nirmatrelvir–ritonavir recipients were dysgeusia (in 6.7% of the 4.0%), and nausea (in 3.1%); the corresponding percentages of placebo recipients with the and 2.7%.

A total of 83 participants (12.7%) had adverse events that were considered by the investigator to be related to nirmatrelvir–ritonavir, as compared with 31 (4.9%) with adverse events that were considered to be related to placebo; the difference was primarily due to higher percentages of participants in the nirmatrelvir–ritonavir group than in the placebo group having dysgeusia (5.8% vs. 0.2%) and diarrhea (2.1% vs. 1.3%). Adverse events and treatment-related adverse events of grade 3 or higher and all serious adverse events are summarized in Tables S5, S6, and S7.

TABLE 3

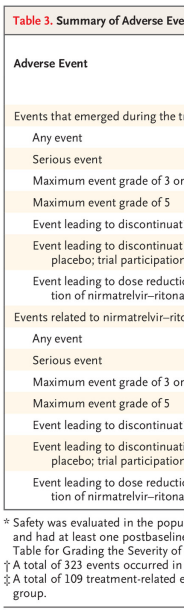


Table 3. Summary of Adverse Eve

Adverse Event
Events that emerged during the t
Any event
Serious event
Maximum event grade of 3 or
Maximum event grade of 5
Event leading to discontinuat
Event leading to discontinuat placebo; trial participation
Event leading to dose reductio tion of nirmatrelvir–ritona
Events related to nirmatrelvir–rito
Any event
Serious event
Maximum event grade of 3 or
Maximum event grade of 5
Event leading to discontinuat
Event leading to discontinuati placebo; trial participation
Event leading to dose reductio tion of nirmatrelvir–ritona

* Safety was evaluated in the popu and had at least one postbaseline Table for Grading the Severity of
† A total of 323 events occurred in
‡ A total of 109 treatment-related e group.

Summary of A

Discussion

criteria were studied. In four of the studies, most of the patient populations were vaccinate administration of booster doses.[12,14–16] The relative effectiveness of nirmatrelvir–ritonavir ranged from 53 to 76% when estimated without consideration of the time from symptom o [12–14,16] Fewer Covid-19–related medical visits were also observed among participants receiv the current trial.

The safety of nirmatrelvir–ritonavir in this trial is consistent with that in the EPIC-HR trial findings. Frequencies of adverse events that emerged during the treatment period, serious events that led to discontinuation were similar in the two groups, with dysgeusia the most nirmatrelvir–ritonavir recipients, followed by diarrhea and nausea.

The limitations of the trial include the statistical analysis of the key secondary end point (C hospitalization or death from any cause), which was only a descriptive analysis because the efficacy end point were not significant. Moreover, participants in the vaccinated high-risk irrespective of the time since their last administered dose of vaccine and irrespective of the vaccination on the efficacy of nirmatrelvir–ritonavir. Given the distinctive taste of nirmatre may have suspected that they were taking that medication, which may have limited the effe Another limitation is that the trial was started during the period of predominance of the B. however, more recent real-world studies have provided evidence for the efficacy of nirmatr CoV-2 variants.[10] As vaccine-induced immunity wanes, new variants emerge, and vaccinati of severe Covid-19–associated outcomes among high-risk patients may increase. The streng enrollment of participants from diverse global locations, which enables generalizability of important, since infections continue to occur even among persons with previous Covid-19

In this trial, we assessed the safety and efficacy of nirmatrelvir–ritonavir as an antiviral age symptomatic, nonhospitalized, vaccinated or unvaccinated adults. Nirmatrelvir–ritonavir v significantly shorter time to sustained alleviation of Covid-19 symptoms than placebo, and nirmatrelvir–ritonavir in patients who are not at high risk for severe Covid-19 has not been

NOTES

A data sharing statement provided by the authors is available with the full text of this article at NEJM.

Supported by Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participants who enrolled in the trial and the staff at the trial sites; the ACTIV2b investi during design of the trial; the following Pfizer colleagues: Charlotte Allerton, Annaliesa Anderson, Je Ayman Ayoub, Karen Baker, Elizabeth Bateman, Arthur Bergman, Mary Boylan Bost, Jade Brennan, K Buckley, Paul Butler, Victoria Butler, Regina Calderon, Rhonda Cardin, Kara Chew, Kristopher Chrisn Cowan, Donna Cox, Bharat Damle, Gretchen Dean, Vanessa Dell, Mikael Dolsten, Elizabeth Dushin,

Protocol (nejmoa2309003_protocol.pdf)

DOWNLOAD 1.66 MB

Supplementary Appendix (nejmoa230900

DOWNLOAD 391.09 KB

Disclosure Forms (nejmoa2309003_disclosures.pdf)

DOWNLOAD 1.36 MB

Data Sharing Statement (nejmoa2309003

DOWNLOAD 70.28 KB

REFERENCES

1. He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019: a systematic re
Virol 2021;93:820-830.

Go to Citation Crossref PubMed ISI Google Scholar

2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (
summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JA*

+ Show Citations Crossref PubMed ISI Google Scholar

3. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mo
identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveill
Infect Dis 2021;72(9):e206-e214.

+ Show Citations Crossref PubMed ISI Google Scholar

4. Docherty AB, Harrison EM, Green CA, et al. Features of 20133 UK patients in hospital with covid-19 u
Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985-m1985.

+ Show Citations Crossref PubMed ISI Google Scholar

5. Thakur B, Dubey P, Benitez J, et al. A systematic review and meta-analysis of geographic differences
severity and mortality among individuals with COVID-19. *Sci Rep* 2021;11:8562-8562.

+ Show Citations Crossref PubMed ISI Google Scholar

Trial of Lixisenatide in Early Parkinson's Disease

W.G. Meissner and Others

ORIGINAL ARTICLE | APR 04, 2024 | CME

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

J. de Boniface and Others