ORIGINAL ARTICLE

# Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

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## ABSTRACT

### BACKGROUND

New treatments are needed to reduce the risk of progression of coronavirus disease 2019 (Covid-19). Molnupiravir is an oral, small-molecule antiviral prodrug that is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

### METHODS

We conducted a phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms in nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19 and at least one risk factor for severe Covid-19 illness. Participants in the trial were randomly assigned to receive 800 mg of molnupiravir or placebo twice daily for 5 days. The primary efficacy end point was the incidence hospitalization or death at day 29; the incidence of adverse events was the primary safety end point. A planned interim analysis was performed when 50% of 1550 participants (target enrollment) had been followed through day 29.

### RESULTS

A total of 1433 participants underwent randomization; 716 were assigned to receive molnupiravir and 717 to receive placebo. With the exception of an imbalance in sex, baseline characteristics were similar in the two groups. The superiority of molnupiravir was demonstrated at the interim analysis; the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). In the analysis of all participants who had undergone randomization, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1). Results of subgroup analyses were largely consistent with these overall results; in some subgroups, such as patients with evidence of previous SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes, the point estimate for the difference favored placebo. One death was reported in the molnupiravir group and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group and 231 of 701 (33.0%) in the placebo group.

### CONCLUSIONS

Early treatment with molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with Covid-19. (Funded by Merck Sharp and Dohme; MOVe-OUT ClinicalTrials.gov number, NCT04575597.)

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*The members of the MOVe-OUT study group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on December 16, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2116044

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has seen almost 270 million confirmed cases and over 5.2 million reported deaths worldwide.[1] A substantial portion of patients with Covid-19 need hospitalization, predominantly older adults and persons with preexisting conditions (e.g., obesity, diabetes mellitus, and serious cardiac conditions).[2-4] Several vaccines that are highly effective in reducing the incidence of hospitalization and death have been authorized; however, vaccine coverage remains insufficient.[5,6] Antiviral therapies that reduce the risk of Covid-19 progression are needed. Since trials have shown the need for initiation of treatment as soon as possible after the onset of symptoms,[7-9] such therapies would ideally be readily available and easily administered by the patients themselves.[10,11]

Molnupiravir is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC), which has activity against SARS-CoV-2 and other RNA viruses and a high barrier to development of resistance.[12-19] After oral administration of molnupiravir, NHC circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is incorporated into viral RNA by viral RNA polymerase and subsequently misdirects the viral polymerase to incorporate either guanosine or adenosine during viral replication. This leads to an accumulation of deleterious errors throughout the viral genome that ultimately render the virus noninfectious and unable to replicate.[14,18,20-22]

Molnupiravir was evaluated in several phase 1 and 2 trials.[10,23,24] On the basis of exposure–response analyses from phase 2 trials, an 800-mg dose of molnupiravir was selected for further investigation,[25] including evaluation in phase 3 of the MOVe-OUT trial in at-risk, nonhospitalized adults in whom the onset of signs or symptoms of Covid-19 had occurred not more than 5 days earlier. Here we report efficacy and safety results from the phase 3 component of the MOVe-OUT trial.

## METHODS

### TRIAL DESIGN AND RANDOMIZATION

The phase 3 component of MOVe-OUT, a phase 2–3, double-blind, parallel-group, randomized, placebo-controlled trial evaluating the safety and efficacy of molnupiravir in nonhospitalized adults with Covid-19, was initiated on May 6, 2021, when the first participant was screened. On the basis of positive efficacy results from a planned interim analysis performed when 50% of 1550 participants (target enrollment) had been followed through day 29 (achieved on September 10, 2021), an independent data monitoring committee recommended that recruitment be stopped early. Recruitment had been ongoing during the interim analysis review; the final participant was enrolled on October 2, 2021, and completed the day 29 visit on November 4, 2021.

Nonhospitalized adults with mild or moderate Covid-19 were eligible; mild or moderate illness was determined on the basis of definitions adapted from Food and Drug Administration[26] and World Health Organization (WHO) guidance.[27] Key inclusion criteria at randomization were SARS-CoV-2 infection that had been laboratory-confirmed no more than 5 days earlier, onset of signs or symptoms no more than 5 days earlier, at least one sign or symptom of Covid-19, and at least one risk factor for development of severe illness from Covid-19 (age >60 years; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity, defined by a body-mass index [the weight in kilograms divided by the square of the height in meters] ≥30; serious heart conditions [heart failure, coronary artery disease, or cardiomyopathies]; or diabetes mellitus). Key exclusion criteria were an anticipated need for hospitalization for Covid-19 within the next 48 hours, dialysis or estimated glomerular filtration rate less than 30 ml per minute per 1.73 $m^2$, pregnancy, unwillingness to use contraception during the intervention period and for at least 4 days after completion of the regimen, severe neutropenia (absolute neutrophil count of <500 per milliliter), platelet count below 100,000 per microliter, and SARS-CoV-2 vaccination. Standard-of-care treatment with antipyretic agents, antiinflammatory agents, glucocorticoids, or a combination was permitted; use of therapies intended as Covid-19 treatments (including any monoclonal antibodies and remdesivir) was prohibited through day 29. Detailed eligibility criteria are listed in the protocol, available with the full text of this article at NEJM.org.

Eligible participants were randomly assigned



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in a 1:1 ratio through the use of a centralized, interactive-response technology system to receive either molnupiravir (800 mg delivered as four 200-mg capsules) or identical placebo, administered orally twice daily for 5 days. Randomization was stratified in blocks of four according to the time since onset of signs or symptoms (≤3 days vs. >3 days). Participants and investigators will remain unaware of the treatment assignments until all actively enrolled participants have undergone the 7-month follow-up visit.

### OVERSIGHT

The trial is being conducted in accordance with Good Clinical Practice guidelines and was approved by the appropriate institutional review boards, ethics committees, and regulatory agencies. Written informed consent was obtained from all the participants. The trial was designed by representatives of the sponsor. Safety oversight was performed by the sponsor and an independent data monitoring committee. Data were collected by the investigators and site personnel, analyzed by statisticians employed by the sponsor, and interpreted by the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### ASSESSMENTS

Vaccination status was reported by the participants. The presence of baseline SARS-CoV-2 nucleocapsid antibodies was assessed centrally with the Elecsys assay (Roche Diagnostics). Covid-19 signs and symptoms were reported as not present, mild, moderate, or severe by participants daily, from randomization through day 29, in paper diaries. A list of all 15 signs and symptoms is provided in the protocol. Nasopharyngeal swabs to be used for quantitation of SARS-CoV-2 RNA through the use of polymerase-chain-reaction assay and for baseline viral genotyping through the use of next-generation sequencing, both performed at a central laboratory, were collected on days 1, 3, 5 (end-of-treatment visit), 10, 15, and 29; assessments of hospitalization status and vital signs, laboratory tests, and physical examinations were also performed on those days. Adverse events were assessed during the treatment period and for 14 days after the end of the treatment period; data on serious adverse events considered by the investigator to be related to the assigned regimen were collected through the end of study participation.

### END POINTS

The primary efficacy end point was the incidence of hospitalization for any cause (defined as ≥24 hours of acute care in a hospital or any similar facility) or death through day 29 in the modified intention-to-treat population, which consisted of all participants who had undergone randomization, had received at least one dose of molnupiravir or placebo, and were not hospitalized before the first dose. Every effort was made to ascertain survival and hospitalization status through day 29 for participants who discontinued participation early. The primary safety end point was the incidence of adverse events. Safety outcomes, including percentages of participants with adverse events, were evaluated in the safety population, which consisted of all participants who had undergone randomization and had received at least one dose of molnupiravir or placebo. Participants were evaluated for any postbaseline platelet levels below 50,000 per microliter and for potential drug-induced liver injury according to prespecified changes in liver enzymes (see the protocol for details).

Secondary efficacy end points were based on the WHO 11-point Clinical Progression Scale and on patients' reported Covid-19 signs and symptoms through day 29. Improvement (i.e., abatement) and progression of Covid-19 signs and symptoms were defined as any reduction and worsening, respectively, of baseline symptom severity. The time to sustained resolution or abatement of signs or symptoms was defined as the number of days from randomization to the first of 3 consecutive days of resolution or alleviation (without subsequent relapse by day 29) and the time to progression of signs or symptoms as the number of days from randomization to the first of 2 consecutive days of worsening. Exploratory end points included mean changes in SARS-CoV-2 viral load from baseline.

### STATISTICAL ANALYSIS

Formal evaluation through hypothesis testing of the efficacy of molnupiravir as compared with placebo was based on the difference (molnupiravir minus placebo) in the percentages of participants meeting the primary efficacy end point,



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assessed through the stratified (by the time of onset of signs or symptoms: ≤3 days vs. >3 days) Miettinen and Nurminen method, which was used to calculate the adjusted risk difference and associated 95% confidence intervals for analysis using Cochran–Mantel–Haenszel weights.[28] The planned enrollment of 1550 participants was selected to ensure greater than 95% power to demonstrate superiority in the primary end point at a one-sided 2.5% alpha level if the underlying event rates were 6% with molnupiravir and 12% with placebo. Missing mortality status at day 29 was imputed as hospitalization or death. All time-to-event analyses were conducted with use of the stratified log-rank test and a Cox proportional hazards model. Changes from baseline in $\log_{10}$ SARS-CoV-2 RNA titer were estimated with constrained longitudinal analysis models, allowing adjustment for differences in mean baseline RNA titers. All analyses were conducted with the use of SAS, version 9.4 (SAS Institute).

A prespecified interim analysis for early efficacy or futility was planned to occur once 50% of the 1550 participants (target enrollment) had been followed through day 29. This analysis was based on the primary efficacy end point according to prospectively set stopping boundaries that were reviewed by regulatory agencies. To maintain control of the type I error at an overall one-sided level of 0.025, the efficacy boundaries for evaluation of the primary end point were determined with the use of the gamma family alpha-spending function, with $\gamma$ equal to –1.[29] At the time of the interim analysis, a one-sided P value of less than 0.0092 was needed to demonstrate early efficacy (superiority of molnupiravir over placebo) on the basis of the prespecified alpha-spending function. No additional hypothesis testing was planned or performed. Efficacy and safety results of this interim analysis were reviewed by the independent data monitoring committee. Because the efficacy results at the interim analysis met the statistical criterion for superiority over placebo, no additional formal statistical testing was planned for the primary efficacy end point. Efficacy data for all participants in the phase 3 population (i.e., the all-randomized sample) are also reported. In addition to prespecified subgroup analyses for the primary end point, we conducted post hoc subgroup analyses according to SARS-CoV-2 clade designation (variant) and baseline risk factor.

## RESULTS

### PARTICIPANTS

The planned interim analysis included 775 participants (comprising 54.1% of the all-randomized sample) who were enrolled at 78 sites in 15 countries and underwent randomization (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The final, all-randomized analysis sample included a total of 1433 participants who were enrolled at 107 sites in 20 countries and underwent randomization (Fig. 1 and Table S1). With the exception of sex, baseline demographic and clinical characteristics were generally similar in the two groups at the time of both the interim analysis (Table S2) and the all-randomized analysis (Table 1 and Table S3). More women were randomly assigned to molnupiravir, and the imbalance was larger in the interim analysis sample (difference, 7.6 percentage points) than in the all-randomized sample (difference, 4.7 percentage points). The participants were largely representative of the expected patient population (Table S4). Overall, 47.7% of the participants had had onset of signs or symptoms 3 days or less before randomization and 44.5% had moderate Covid-19. The most common risk factors were obesity (73.7%), age over 60 years (17.2%), and diabetes mellitus (15.9%). SARS-CoV-2 nucleocapsid antibodies at baseline, indicating recent or previous infection (not vaccination), were reported among 19.8% of participants. Owing to the ongoing nature of testing, 25.9% of the participants in the interim analysis sample did not have baseline sequence data available, and 44.7% in the all-randomized sample did not have baseline sequence data available at the time of this report. Among all participants who underwent randomization and had sequence data available, the three most common SARS-CoV-2 variants were B.1.617.2 (delta; 58.1%), B.1.621 (mu; 20.5%), and P.1 (gamma; 10.7%). Almost all the participants (98.3%; 709 in the molnupiravir group and 699 in the placebo group) were included in the modified intention-to-treat population (Fig. 1). Among those who received molnupiravir or placebo, most (95.2% in the molnupiravir group and 94.7% in the placebo group)



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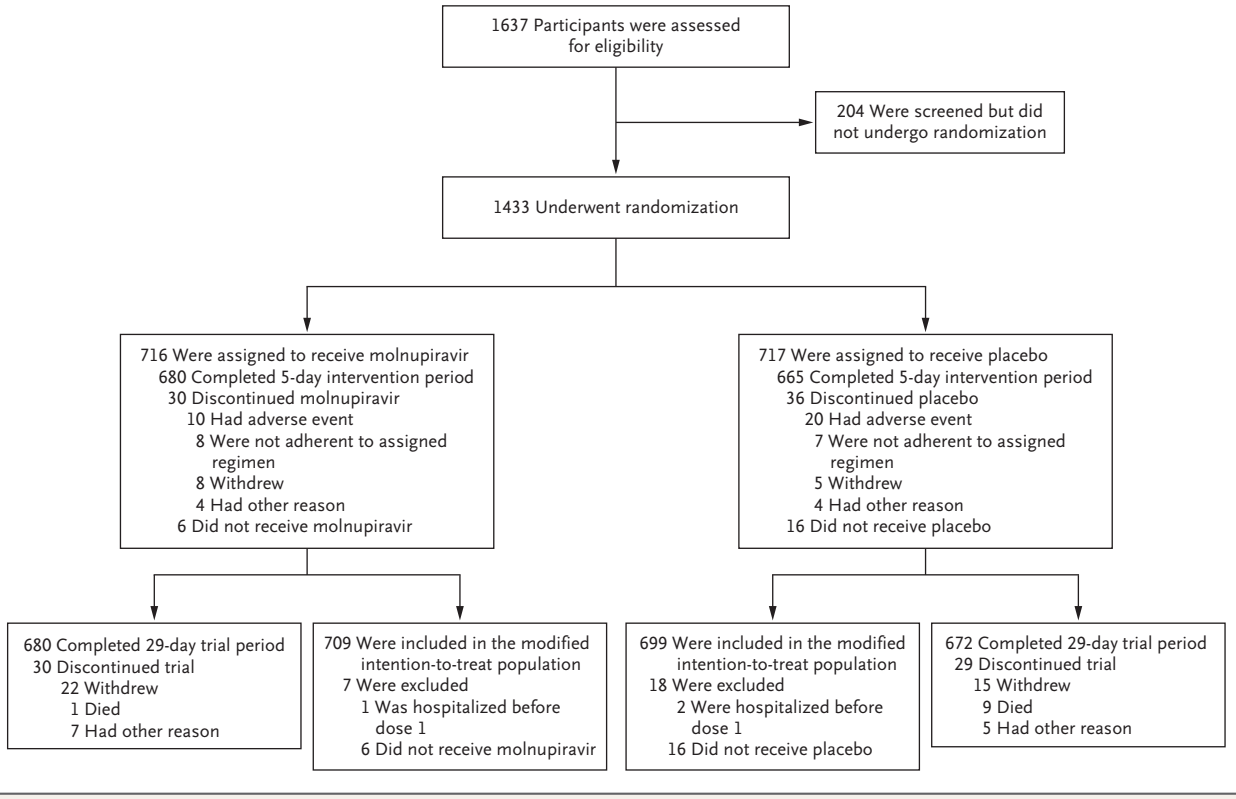


**Figure 1. Randomization and Flow of Participants from Baseline through Day 29.**

received at least 9 doses. Survival status at day 29 was confirmed for all but a single participant in the modified intention-to-treat population, including participants who discontinued the trial early; this single participant (in the placebo group), whose hospitalization status at day 29 was also unknown, was the only one for whom the primary end point was imputed as hospitalized or dead. For two additional participants, hospitalization status at day 29 could not be determined; these participants were confirmed to be alive at day 29 and were therefore counted as alive and not hospitalized through day 29, in accordance with the prespecified analysis plan.

### EFFICACY

Molnupiravir met the prespecified superiority criterion at the time of the interim analysis; at day 29, the percentage of participants in the modified intention-to-treat population who had been hospitalized or had died was significantly lower in the molnupiravir group (7.3% [28 of 385 participants]) than in the placebo group (14.1% [53 of 377 participants), a treatment difference of 6.8 percentage points (95% confidence interval [CI], −11.3 to −2.4; P=0.001). In the all-randomized modified intention-to-treat population, participants receiving molnupiravir had a lower risk of hospitalization or death through day 29: 6.8% (48 of 709 participants) in the molnupiravir group as compared with 9.7% (68 of 699 participants) in the placebo group (difference, 3.0 percentage points; 95% CI, −5.9 to −0.1). A prespecified supporting analysis specifically evaluating only Covid-19–related hospitalizations or deaths (Fig. S2) showed that 45 of 709 participants (6.3%) in the molnupiravir group and 64 of 699 (9.2%) in the placebo group had hospitalizations or deaths that were considered by the investigators to be Covid-19–related (difference, 2.8 percentage points; 95% CI, −5.7 to 0.0). The results of a post hoc analysis adjusted for participant sex (the only baseline factor potentially unbalanced between the groups) were consistent



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**Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.***

| Characteristic | Molnupiravir (N=716) | Placebo (N=717) | Total (N=1433) |
|---|---|---|---|
| Female sex — no. (%) | 384 (53.6) | 351 (49.0) | 735 (51.3) |
| Age group — no. (%) | | | |
| 18–49 yr | 484 (67.6) | 465 (64.9) | 949 (66.2) |
| ≥50 yr | 232 (32.4) | 252 (35.1) | 484 (33.8) |
| Median age (range) — yr | 42.0 (18–90) | 44.0 (18–88) | 43.0 (18–90) |
| Risk factors for severe illness from Covid-19 — no. (%) | | | |
| At least one risk factor | 712 (99.4) | 712 (99.3) | 1424 (99.4) |
| Obesity† | 538 (75.1) | 518 (72.2) | 1056 (73.7) |
| Age >60 yr | 119 (16.6) | 127 (17.7) | 246 (17.2) |
| Diabetes mellitus | 107 (14.9) | 121 (16.9) | 228 (15.9) |
| Serious heart condition | 86 (12.0) | 81 (11.3) | 167 (11.7) |
| Chronic kidney disease | 38 (5.3) | 46 (6.4) | 84 (5.9) |
| Chronic obstructive pulmonary disease | 22 (3.1) | 35 (4.9) | 57 (4.0) |
| Active cancer | 13 (1.8) | 16 (2.2) | 29 (2.0) |
| Covid-19 severity — no. (%) | | | |
| Mild | 395 (55.2) | 390 (54.4) | 785 (54.8) |
| Moderate | 315 (44.0) | 323 (45.0) | 638 (44.5) |
| Severe or unknown‡ | 6 (0.8) | 4 (0.6) | 10 (0.7) |
| Clade designation; variant — no. (%) | | | |
| 20H; beta | 5 (0.7) | 6 (0.8) | 11 (0.8) |
| 20I; alpha | 12 (1.7) | 9 (1.3) | 21 (1.5) |
| 20J; gamma | 37 (5.2) | 48 (6.7) | 85 (5.9) |
| 21A, 21I, 21J; delta | 237 (33.1) | 223 (31.1) | 460 (32.1) |
| 21G; lambda | 14 (2.0) | 7 (1.0) | 21 (1.5) |
| 21H; mu | 76 (10.6) | 86 (12.0) | 162 (11.3) |
| Other§ | 16 (2.2) | 16 (2.2) | 32 (2.2) |
| Evaluable sequence data not yet available | 319 (44.6) | 322 (44.9) | 641 (44.7) |
| Time from onset of Covid-19 signs or symptoms to randomization of ≤3 days — no. (%)¶ | 342 (47.8) | 342 (47.7) | 684 (47.7) |
| SARS-CoV-2 RNA in nasopharyngeal sample, qualitative assay — no. (%)‡ | | | |
| Detectable | 615 (85.9) | 615 (85.8) | 1230 (85.8) |
| Undetectable | 54 (7.5) | 51 (7.1) | 105 (7.3) |
| SARS-CoV-2 nucleocapsid antibody — no. (%)‡‖ | | | |
| Positive | 137 (19.1) | 147 (20.5) | 284 (19.8) |
| Negative | 541 (75.6) | 521 (72.7) | 1062 (74.1) |

* Participants are those who underwent randomization.
† Obesity was defined by a body-mass index of 30 or higher.
‡ Missing data, invalid samples, tests not done, or results reported as "unknown" are all categorized as unknown and are not shown individually (see Table S3 in the Supplementary Appendix for details).
§ "Other" includes the following clades: 19B, 20A, 20B, 20C, 20D, and unknown clades or those that could not be classified.
¶ The time period was based on data collected at randomization.
‖ Data are based on nucleocapsid antibody assay and do not reflect prior vaccination status, since Covid-19 vaccines generate antibodies against the SARS-CoV-2 spike protein, not the SARS-CoV-2 nucleocapsid protein.



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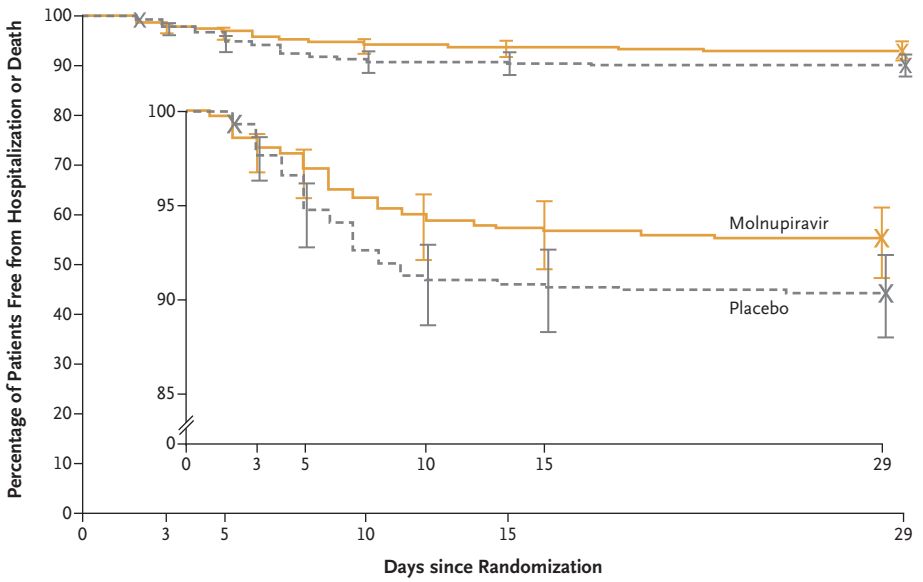


| | | | | | | |
|---|---|---|---|---|---|---|
| **No. at Risk** | | | | | | |
| Molnupiravir | 709 | 699 | 693 | 670 | 665 | 661 |
| Placebo | 699 | 693 | 674 | 637 | 634 | 631 |
| **No. of Events** | | | | | | |
| Molnupiravir | 10 | 6 | 23 | 5 | 4 | 0 |
| Placebo | 5 | 19 | 37 | 3 | 3 | 0 |

**Figure 2. Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population.**

Shown are Kaplan–Meier curves with 95% confidence intervals (I bars). X indicates censored values. Data for the single participant with unknown survival status and no hospitalization reported were censored on the day when the participant was last known to be alive. The inset shows the same data on an expanded y axis.

with those of the primary analysis, with a risk of hospitalization or death through day 29 that was lower by 2.8 percentage points (95% CI, –5.7 to 0.1) with molnupiravir over placebo. The results of a time-to-event analysis were also consistent with the primary results; the rate of hospitalization or death through day 29 was approximately 31% lower with molnupiravir than with placebo (hazard ratio, 0.69; 95% CI, 0.48 to 1.01) (Fig. 2). One death was reported in the molnupiravir group (29-day all-cause mortality, 0.1%) and 9 deaths in the placebo group (29-day all-cause mortality, 1.3%) (Fig. S2), a risk of death that was lower by 89% (95% CI, 14 to 99) with molnupiravir than with placebo. All 10 participants had been hospitalized before death, and all the deaths were considered by the investigators to be Covid-19–related. In most prespecified subgroups, the percentage of participants who were hospitalized or died was lower with molnupiravir than placebo, but the associated confidence intervals indicate substantial uncertainty about the magnitude of these effects (Fig. 3). The point estimate for the difference in the risk of hospitalization or death through day 29 favored placebo over molnupiravir only in patients with SARS-CoV-2 nucleocapsid antibodies at baseline; patients with low viral load at baseline; patients with diabetes at baseline; patients who identified themselves as Asian only, Black only, Native American only, or mixed Black–Native American–White; and patients enrolled in the Asia-Pacific region; all the associated 95% confidence intervals included zero and some were fairly wide, particularly because some of these subgroups had small sample sizes (Fig. S3). Because sequencing for baseline clade is still ongoing, outcomes according to causative SARS-CoV-2 variant were available for only 55.7% of all modified intention-to-treat participants at the time of this report; subgroup analyses according to baseline variants for those with available data are shown in Fig. S3.



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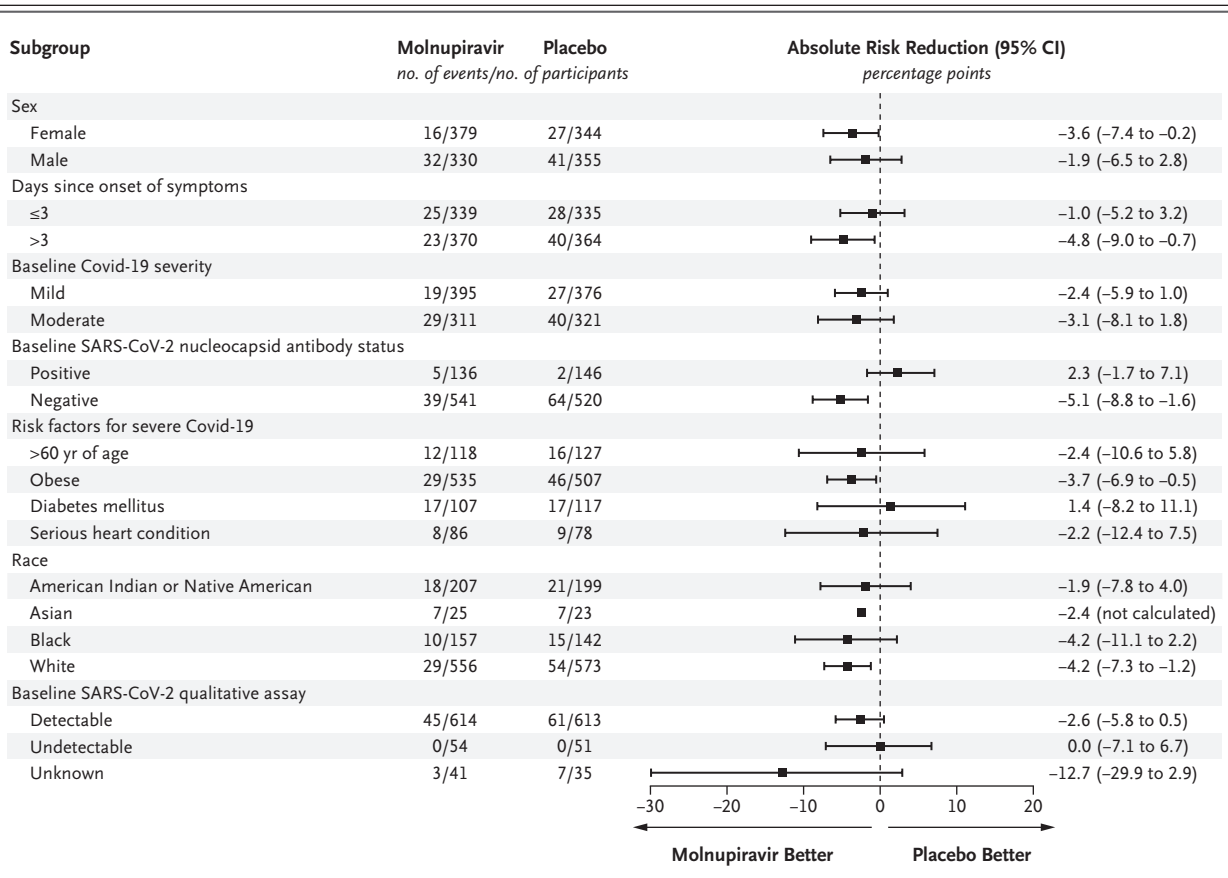


**Figure 3. Incidence of Hospitalization or Death at Day 29 in the Modified Intention-to-Treat Population, According to Subgroup.**

Shown are data for the primary end point in key subgroups of the modified intention-to-treat population. The 95% confidence intervals are based on the unstratified Miettinen and Nurminen method. Obesity was defined by a body-mass index of 30 or above. Data on baseline nucleocapsid antibody status are based on a nucleocapsid antibody assay and do not reflect previous vaccination status, since Covid-19 vaccines generate antibodies against the SARS-CoV-2 spike protein, not the SARS-CoV-2 nucleocapsid protein. Race and ethnic group were reported by the participants, who identified themselves from a set of available options. Each race or ethnic group category includes participants who identified themselves as belonging to that race or ethnic group only or as belonging to that race or ethnic group plus one or more other races or ethnic groups; thus, participants could be counted in more than one race or ethnic group category. Confidence intervals were not adjusted for multiple comparisons and may not be reproducible. For the Asian race group, the confidence interval was not calculated, in accordance with the analysis plan, owing to a sample size of less than 25 participants in either group. (See Fig. S3 for details on race and ethnic group.) Outcomes according to baseline clade are not shown here, since at the time of this report, clade sequencing had not yet been conducted for about 45% of all participants who underwent randomization.

On the basis of the WHO Clinical Progression Scale, a greater percentage of participants in the molnupiravir group than in the placebo group showed improved outcomes by day 5, with the largest differences observed by days 10 and 15 (Table S5). For most Covid-19 signs and symptoms, sustained abatement or resolution was more likely (Fig. S4) and progression of signs or symptoms was less likely (Fig. S5) in the molnupiravir group than in the placebo group.

### VIROLOGY

At the time of the all-randomized analysis, 1093 of 1408 participants (77.6%) in the modified intention-to-treat population had quantifiable RNA confirmed in nasopharyngeal samples at baseline, and of those, samples from 964 participants (88.2%) had been tested at day 5; because this was an exploratory outcome, testing is ongoing. On the basis of the available data, molnupiravir treatment was associated with greater



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**Table 2. Incidence of Adverse Events in the Safety Population.**

| Adverse Events and Discontinuation | Molnupiravir (N = 710) | Placebo (N = 701) | Estimated Difference (95% CI)* |
|---|---|---|---|
| | *number (percent)* | | *percentage points* |
| Participants with adverse events | | | |
| ≥1 Adverse event | 216 (30.4) | 231 (33.0) | −2.5 (−7.4 to 2.3) |
| ≥1 Adverse event related to the assigned regimen† | 57 (8.0) | 59 (8.4) | −0.4 (−3.3 to 2.5) |
| ≥1 Serious adverse event | 49 (6.9) | 67 (9.6) | −2.7 (−5.6 to 0.2) |
| ≥1 Serious adverse event related to the assigned regimen† | 0 | 1 (0.1) | −0.1 (−0.8 to 0.4) |
| Death | 2 (0.3) | 12 (1.7) | −1.4 (−2.7 to −0.5) |
| Participants who discontinued the assigned regimen because of an adverse event | | | |
| Adverse event | 10 (1.4) | 20 (2.9) | −1.4 (−3.1 to 0.1) |
| Adverse event related to the assigned regimen† | 4 (0.6) | 3 (0.4) | 0.1 (−0.8 to 1.1) |
| Serious adverse event | 5 (0.7) | 13 (1.9) | −1.2 (−2.5 to 0.0) |
| Serious adverse event related to the assigned regimen† | 0 | 0 | 0.0 (−0.5 to 0.5) |

* Differences shown are for molnupiravir as compared with placebo. Difference estimates were based on the Miettinen and Nurminen method.
† Related events were those determined by the investigators to be related to the assigned regimen.

reductions from baseline in mean viral load than placebo at days 3, 5 (end-of-treatment visit), and 10 (Fig. S6 and Table S6). Results at other time points were similar in the two groups.

### SAFETY

The percentage of participants with at least one adverse event was similar in the two groups (30.40% in the molnupiravir group and 33.0% in the placebo group), as was the percentage of participants with adverse events considered by the investigators to be related to the trial regimen (8.0% vs. 8.4%). Deaths resulting from adverse events, none of which were deemed by the investigators to be related to the trial regimen, were reported less frequently in the molnupiravir group than in the placebo group (Table 2). After day 29, three additional deaths resulting from adverse events occurred in the placebo group, as compared with one additional death reported in the molnupiravir group.

The most frequently reported adverse events (those that occurred in ≥2% of participants in either group) were Covid-19 pneumonia (which occurred in 6.3% of participants in the molnupiravir group as compared with 9.6% of those in the placebo group), diarrhea (2.3% vs. 3.0%), and bacterial pneumonia (2.0% vs. 1.6%); worsening of Covid-19 was reported as an adverse event in 7.9% as compared with 9.8%. The most frequently reported adverse events (occurring in ≥1% of participants in either group) that were deemed to be related to the trial regimen were diarrhea (1.7% vs. 2.1%), nausea (1.4% vs. 0.7%), and dizziness (1.0% vs. 0.7%). One participant each in the molnupiravir and placebo groups met the prespecified criteria for a postbaseline platelet count below 50,000 per microliter; the low platelet count in the molnupiravir-treated participant was reported on day 12 and was not deemed to be related to treatment.

## DISCUSSION

These data from the MOVe-OUT phase 3 trial in nonhospitalized at-risk adults with Covid-19 indicate that molnupiravir, initiated within 5 days after the onset of symptoms, reduces the risk of hospitalization for any cause or death through day 29. The trial population was representative



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of real-world patients with one or more well-established risk factors for severe illness due to Covid-19.[2-4,30] Of note, in published clinical trials evaluating monoclonal antibody treatments in similar populations of nonhospitalized, at-risk patients with Covid-19, the incidence of hospitalization or death with placebo was reported to be about 3 to 7%. In comparison, the incidence in our trial was 14% at the interim analysis and 10% in the all-randomized analysis, which suggests that the participants enrolled in our trial were at higher risk for disease progression. The risk of hospitalization or death at day 29 was 6.8 percentage points lower with molnupiravir than with placebo at the interim analysis and 3.0 percentage points lower in the all-randomized analysis, an improvement in an outcome that is potentially meaningful for patients, health care systems, and public health. In an analysis that was not adjusted for multiplicity, the efficacy benefit with molnupiravir treatment was consistent in many subgroups, including participants infected with the delta, gamma, and mu variants of SARS-CoV-2 according to the available baseline clade data. Since virology outcomes were exploratory, some nasopharyngeal samples, particularly those from later time points, were still awaiting analysis as of this writing; the pending analyses do not represent data that were missing because of death or discontinuation of a trial regimen, but estimates for the associated risk differences may change as additional baseline clade data continue to become available. Outcomes did not appear to be better with molnupiravir than with placebo in several subgroups (some of relatively small sample size), including patients with evidence of previous SARS-CoV-2 infection, patients with low baseline viral load, and patients with diabetes mellitus; in all cases the 95% confidence intervals of the estimated risk differences included zero. Secondary end points, including changes in the WHO Clinical Progression Scale and in patient-reported symptoms of Covid-19, also indicated clinical benefits with molnupiravir over placebo. As in previous trials,[7,10,23,24,31] no safety concerns with molnupiravir were identified and there was no evidence of a pattern of clinically meaningful abnormalities in laboratory test results. Since pregnancy was an exclusion criterion in this trial, the potential impact of molnupiravir on fetal development is unknown.

Given the compelling efficacy and safety results obtained at the time of the interim analysis, the independent data monitoring committee recommended an early stop to recruitment of new participants in the trial. Further enrollment was halted, at which point 1433 participants (92% of the planned 1550 participants) had already undergone randomization. The planned interim analysis, in which efficacy results met the statistical criterion for superiority over placebo, represented the formal evaluation of efficacy for the trial; in accordance with the prespecified analysis plan, no additional statistical testing was performed for the primary efficacy end point. The point estimate for the treatment difference was lower in analyses of all participants who underwent randomization than in the interim analysis. The incidence of hospitalization or death in the all-randomized sample remained consistent in the molnupiravir group but fell in the placebo group as compared with the interim analysis sample. The reasons for this difference are unknown, but potential contributing factors include imbalances between the analysis samples, shifts in the epidemiology of the Covid-19 pandemic, and regional variation among the enrolled participants. A comparison of patient characteristics does not suggest a clear, single cause for the difference between the interim and the all-randomized analyses, which may have been the result of the accumulation of lesser effects of multiple factors. For instance, in the placebo group of the all-randomized sample there were somewhat more female patients (who have a lower risk of severe Covid-19 than male patients), more participants with SARS-CoV-2 nucleocapsid antibodies (which also suggests a lower risk), and more participants with low viral load at baseline (in whom there is less virologic effect) than at the time of the interim analysis. All these factors may have contributed to a lower overall event rate in the placebo group in the all-randomized sample than in the interim analysis. In addition, the all-randomized sample included newly enrolling countries with different hospitalization practices or hospital capacity, which may also have affected hospitalization rates as part of the primary outcome. The effect



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of the public release statement of efficacy after the interim analysis on the all-randomized efficacy outcome is unknown. Despite the reduced treatment effect estimate for the primary end point in the all-randomized analysis as compared with the interim analysis, treatment with molnupiravir was efficacious across this broad, rapidly changing data set and appeared to yield a substantial mortality benefit.

Many patients with Covid-19 recover from their acute infection with no or minimal medical intervention.[2,32] However, clinical progression to severe disease has a considerable impact on patients and on health care systems, increasing a patient's risks of receiving mechanical ventilation and of death and potentially overburdening local and regional hospital capacity during Covid-19 surges. Reducing Covid-19–related hospitalizations, and potentially also reducing community transmission by helping patients clear infectious virus more rapidly, are therefore critical. Vaccination remains the most important medical intervention available to lower the risks of hospitalization and death from Covid-19,[30,33,34] but early treatment soon after the onset of symptoms has also been shown to be effective.[8] The monoclonal antibodies bamlanivimab–etesevimab, casirivimab–imdevimab, and sotrovimab are currently authorized treatments for at-risk outpatients with Covid-19.[9,35,36] Because monoclonal antibodies require administration by means of infusion or injection in a medical setting, oral agents such as molnupiravir that can be administered by the patient at home shortly after diagnosis may be more practical and patient-friendly for nonhospitalized persons; such agents would be important new tools in the Covid-19 treatment armamentarium. Another advantage of molnupiravir over SARS-CoV-2 spike protein–directed monoclonal antibodies is the efficacy of molnupiravir against SARS-CoV-2 variants.[12,17,19] The mechanism of action of molnupiravir is independent of mutations in the spike protein, which can affect the efficacy of monoclonal antibody treatments.[8,37,38]

Only patients not vaccinated against Covid-19 were eligible for our trial, a choice made both to focus on those most likely to need antiviral treatment and to facilitate more rapid evaluation of the therapeutic efficacy of molnupiravir. The potential benefit of molnupiravir for the treatment of Covid-19 vaccine breakthrough infections was thus not evaluated; efficacy outcomes in baseline seropositive participants cannot be used to draw relevant conclusions, since the SARS-CoV-2 nucleocapsid antibody assay reflects an immune response to a previous or current infection and does not detect the presence of vaccine-generated, neutralizing antispike antibodies.

In this trial, oral molnupiravir was found to be effective for the treatment of Covid-19, without evident safety concerns, when initiated within 5 days after the onset of signs or symptoms in this population of nonhospitalized, unvaccinated adults who were at risk for progression to severe disease.

Supported by Merck Sharp and Dohme, a subsidiary of Merck, Kenilworth, NJ.

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

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

We thank the participants and their families and caregivers for their participation in this trial and Wendy Painter, M.D., and Wayne Holman, M.D., both of Ridgeback Biotherapeutics, Miami, for scientific discussions. Medical writing assistance was provided by Dominik J. Wolf, M.Sc., who wrote the first draft of the manuscript under guidance from the authors, and editorial assistance was provided by Karyn Davis, B.S., both of Merck Sharp and Dohme, a subsidiary of Merck, Kenilworth, NJ.

## APPENDIX

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