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Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19

A Randomized, Placebo-Controlled Trial

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Background: In the MOVe-OUT trial, molnupiravir showed a clinically meaningful reduction in the risk for hospitalization or death in adults with mild to moderate COVID-19 and risk factors for progression to severe disease.

Objective: To identify other potential clinical benefits of molnupiravir versus placebo.

Design: Secondary analysis of the randomized, double-blind, placebo-controlled phase 3 component of MOVe-OUT. (ClinicalTrials.gov: NCT04575597)

Setting: 107 sites globally.

Participants: 1433 nonhospitalized adults aged 18 years or older with mild to moderate COVID-19.

Intervention: Molnupiravir, 800 mg, or placebo every 12 hours for 5 days.

Measurements: Changes from baseline in C-reactive protein (CRP) concentration and oxygen saturation (SpO_2), need for respiratory interventions (including invasive mechanical ventilation), and need for medical services in all randomly assigned participants through day 29, and need for respiratory interventions and time to discharge in the subgroup of participants who were hospitalized after randomization.

Results: Participants receiving molnupiravir showed faster normalization of CRP and SpO_2, with improvements observed on day 3 of therapy, compared with placebo. Molnupiravir-treated participants had a decreased need for respiratory interventions versus placebo-treated participants (relative risk reduction [RRR], 34.3% [95% CI, 4.3% to 54.9%]), with similar findings in participants who were hospitalized after randomization (RRR, 21.3% [CI, 0.2% to 38.0%]). Hospitalized participants who received molnupiravir were discharged a median of 3 days before those who received placebo. Acute care visits (7.2% vs. 10.6%; RRR, 32.1% [CI, 4.4% to 51.7%]) and COVID-19–related acute care visits (6.6% vs. 10.0%; RRR, 33.8% [CI, 5.6% to 53.6%]) were less frequent in molnupiravir- versus placebo-treated participants.

Limitations: Some analyses were performed post hoc. Longer-term benefits of molnupiravir therapy were not evaluated. Participants were not immunized against SARS-CoV-2.

Conclusion: The findings suggest there are additional important clinical benefits of molnupiravir beyond reduction in hospitalization or death.

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SARS-CoV-2 is responsible for an unprecedented global pandemic that has resulted in 527 million cases and 6.3 million deaths worldwide as of 31 May 2022 (1, 2). The clinical presentation of SARS-CoV-2 infection varies; some people remain asymptomatic, whereas others develop COVID-19 that can range in severity from mild to critical illness resulting from a hyperinflammatory response to the virus (3, 4). Maintaining the availability of life-saving interventions, such as ventilatory and/or hemodynamic support, for all patients with severe or critical COVID-19 has been a major challenge throughout the pandemic, especially in regions with limited resources at baseline and during COVID-19 surges (5–8).

Immunization for COVID-19 decreases hospitalizations and progression to severe disease (9). However, many people remain unvaccinated due to lack of access or vaccine hesitancy (10, 11), breakthrough infections can occur, and vaccines may need to be modified in response to emerging SARS-CoV-2 variants (12, 13). Some monoclonal antibodies (mAbs) and antivirals have been shown to decrease the risk for hospitalization and/or death compared with placebo in nonhospitalized patients with COVID-19 who have risk factors for progression to severe disease (14–19). The effect of these therapies on other clinically relevant outcomes, such as changes in inflammatory markers, oxygen saturation (SpO_2), or ventilation requirements, in nonhospitalized patients or those requiring hospitalization after receiving these therapies has not been fully elucidated. The implementation of some of these therapies has been challenging (20), limiting their widespread availability and uptake globally. For instance, most mAbs and intravenous remdesivir must be administered in a medical setting (21–25), further burdening health care systems, limiting access for patients, and introducing infection control risks. Moreover, some mAbs are no longer recommended because they

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are ineffective against the Omicron (B.1.1.529) variant, which has been responsible for recent surges (3, 7, 26). The only other oral antiviral currently available, nirmatrelvir–ritonavir, requires careful assessment for drug–drug interactions before use (3, 27). As a result, there remains an unmet need for antiviral therapies that can be easily self-administered in the outpatient setting to not only improve outcomes for patients but also ease the burden of COVID-19 on the health care system.

Molnupiravir is an orally available small-molecule ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC) with potent, broad-spectrum in vitro activity against coronaviruses, including SARS-CoV-2 variants of concern, and a high barrier to the development of resistance (28–38). Molnupiravir is metabolized to NHC by esterases and then phosphorylated intracellularly to the active form, NHC-triphosphate, which is incorporated into the viral genome, ultimately resulting in replication-incompetent SARS-CoV-2 (39, 40). Molnupiravir does not require dose adjustment for renal or hepatic impairment, and in vitro studies indicate that molnupiravir and NHC are not substrates, inhibitors, or inducers of CYP3A4 enzymes (41).

The phase 3 component of the MOVe-OUT clinical trial established the efficacy and safety of molnupiravir in nonhospitalized adults with mild to moderate COVID-19 and risk factors for progression to severe disease. Molnupiravir (800 mg every 12 hours for 5 days, initiated within 5 days of the onset of signs or symptoms of COVID-19) was superior to placebo at the prespecified interim analysis for the primary efficacy end point of all-cause hospitalization or death by day 29 (7.3% vs. 14.1%; difference, −6.8 percentage points [95% CI, −11.3 to −2.4 percentage points]). In the final analysis of all randomly assigned participants, molnupiravir showed a clinically meaningful reduction in the risk for hospitalization or death (6.8% vs. 9.7%; difference, −3.0 percentage points [CI, −5.9 to −0.1 percentage points]), providing evidence of a substantial mortality benefit (89% decreased risk for death), a shorter time to resolution for most COVID-19 signs and symptoms, a greater reduction in mean viral load from baseline, and a lack of safety concerns compared with placebo through day 29 (19).

We conducted additional analyses to evaluate additional potential benefits of molnupiravir for the treatment of mild to moderate COVID-19 based on clinical markers and the need for respiratory interventions and medical services from the phase 3 component of MOVe-OUT. Changes in high-sensitivity C-reactive protein (CRP) concentration, Spo_2, the need for respiratory interventions, acute care visits, and COVID-19–related acute care visits were evaluated in all randomly assigned participants who received molnupiravir or placebo. Respiratory interventions plus time to discharge were assessed in the subgroup of participants who were hospitalized after randomization.

METHODS

Design Overview, Setting, and Participants

MOVe-OUT (ClinicalTrials.gov: NCT04575597) was a phase 2/3 double-blind, parallel-group, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of molnupiravir compared with placebo. Full details of the phase 2 and phase 3 components of MOVe-OUT have been published previously (19, 42). Here, we report on results from the phase 3 component.

Nonhospitalized adults aged 18 years or older with laboratory-confirmed mild to moderate COVID-19 (**Appendix Table 1**, available at Annals.org) were included in the phase 3 component of MOVe-OUT. Participants had to have onset of signs or symptoms no more than 5 days prior and at least 1 risk factor for progression to severe disease. Prespecified risk factors for severe disease were age older than 60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (body mass index ≥30 kg/m^2), serious heart conditions (heart failure, coronary artery disease, or cardiomyopathies), and diabetes mellitus. Key exclusion criteria included an anticipated need for inpatient treatment of COVID-19 within 48 hours, stage 4 or 5 chronic kidney disease or dialysis, pregnancy, and receipt of a SARS-CoV-2 vaccine.

Participants were randomly assigned in a 1:1 ratio to receive molnupiravir, 800 mg, or matching placebo every 12 hours for 5 days, stratified by the time of onset of signs or symptoms (≤3 or >3 days), with the first dose of study drug administered within 24 hours of randomization. Participants could receive supportive care with antipyretics, anti-inflammatory agents, or glucocorticoids at the investigator's discretion, but therapies indicated specifically for COVID-19 (for example, mAbs, remdesivir) were prohibited through day 29. For participants who required hospitalization after randomization, all study procedures and study drug administration were to be continued if possible, and treatment with COVID-19–specific therapies was permitted.

Study visits occurred at screening and on days 1 (baseline), 3, 5 (end of therapy), 10, 15, and 29. All assessments were prespecified in the study protocol (**Supplement**, available at Annals.org) and performed prospectively over the course of the trial. Spo_2 and the need for and type of respiratory intervention were reviewed at screening and at every study visit thereafter. At each study visit, Spo_2 was measured by pulse oximetry after participants rested for at least 5 minutes. Blood samples were collected on day 1 and at all postbaseline study visits for hematology, chemistry, and CRP laboratory measurements. Acute care visits, such as urgent care, office, or clinic visits, and hospitalization status (**Appendix Table 2**, available at Annals.org) were assessed through day 29.

Outcomes

Baseline demographic and clinical characteristics and mean changes in CRP concentration and Spo_2 from baseline through day 29 were evaluated in the safety population, which consisted of all participants who had undergone randomization and had received at least 1 dose of study drug. The use of any respiratory interventions (including conventional oxygen therapy, a high-flow heated and humidified device, noninvasive mechanical ventilation, and invasive mechanical ventilation), acute care visits, and COVID-19–related acute care visits were assessed in the modified intention-to-treat (MITT)

Table. Baseline Demographic and Clinical Characteristics in the Safety Population

Characteristic	Molnupiravir (*n* = 710)	Placebo (*n* = 701)
Female, *n (%)*	380 (53.5)	345 (49.2)
Median age (range), *y*	43 (18–90)	44 (18–88)
Median time from symptom onset to randomization (range), *d*	4 (1–5)	4 (1–5)
Race, *n (%)*		
White	397 (55.9)	405 (57.8)
Multiple	189 (26.6)	197 (28.1)
American Indian or Alaska Native	60 (8.5)	43 (6.1)
Black or African American	39 (5.5)	34 (4.9)
Asian	25 (3.5)	22 (3.1)
Hispanic or Latino, *n (%)*	352 (49.6)*	348 (49.6)†
Region, *n (%)*		
Latin America	330 (46.5)	323 (46.1)
Europe	229 (32.3)	233 (33.2)
Africa	90 (12.7)	84 (12.0)
North America	42 (5.9)	45 (6.4)
Asia-Pacific	19 (2.7)	16 (2.3)
Risk factors for severe COVID-19, *n (%)*		
≥1 risk factor	709 (99.9)	698 (99.6)
Body mass index ≥30 kg/m^2	535 (75.4)	508 (72.5)
Age >60 y	119 (16.8)	127 (18.1)
Diabetes mellitus	107 (15.1)	118 (16.8)
Serious heart condition	86 (12.1)	78 (11.1)
Chronic kidney disease	38 (5.4)	44 (6.3)
Chronic obstructive pulmonary disease	22 (3.1)	34 (4.9)
Active cancer	13 (1.8)	16 (2.3)
COVID-19 severity, *n (%)*		
Mild	395 (55.6)	378 (53.9)
Moderate	312 (43.9)	321 (45.8)
Severe	3 (0.4)	1 (0.1)
Unknown‡	0 (0.0)	1 (0.1)
SARS-CoV-2 RNA qualitative assay, *n (%)*		
Detectable	615 (86.6)	615 (87.7)
Undetectable	54 (7.6)	51 (7.3)
Unknown‡	41 (5.8)	35 (5.0)
SARS-CoV-2 RNA quantitative assay, *n (%)*		
High (>1 000 000 copies/mL)	389 (54.8)	383 (54.6)
Low (500 to ≤1 000 000 copies/mL)	161 (22.7)	163 (23.3)
Undetectable (<500 copies/mL)	64 (9.0)	71 (10.1)
Unknown‡	96 (13.5)	84 (12.0)
SARS-CoV-2 nucleocapsid antibody, *n (%)*		
Positive	137 (19.3)	147 (21.0)
Negative	541 (76.2)	521 (74.3)
Unknown‡	32 (4.5)	33 (4.7)

* Data were not reported or were missing in 6 participants.
† Data were not reported or were missing in 3 participants.
‡ Includes missing data, invalid samples, tests not done, or results reported as unknown.

population. The MITT population included all participants who were randomly assigned, received at least 1 dose of study drug, and were not hospitalized before the first dose of study drug. Participants hospitalized before the first dose were not included in the MITT population because they could not be assessed for the primary efficacy end point. Respiratory interventions along with time to hospital discharge were examined in participants in the MITT population who required hospitalization after randomization.

Statistical Analysis

Acute care visits and COVID-19–related acute care visits were prespecified exploratory end points in the MOVe-OUT study protocol; the analysis plan for these end points was also prespecified. The differences in the proportions for acute care visits and COVID-19–related acute care visits between treatment groups, and their corresponding 95% CIs, were estimated based on the Miettinen–Nurminen method, with stratification by randomization strata (43). The median time to hospital discharge

among participants with observed hospitalization through day 29 was estimated post hoc using the product-limit (Kaplan–Meier) method for censored data. Death and early discontinuation were censored at the time of the event, and participants who completed day 29 with no discharge by that time were censored at day 29. All other analyses presented were performed post hoc, and descriptive statistics were provided for all other outcomes included in this article. Relative risk reductions (RRRs) and their corresponding 95% CIs were calculated as appropriate. All analyses were conducted using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The trial sponsor, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., was involved in the study design; collection, analysis, and interpretation of the data; and writing of the report. All authors had access to the study data and final responsibility for the decision to submit the manuscript for publication.

RESULTS

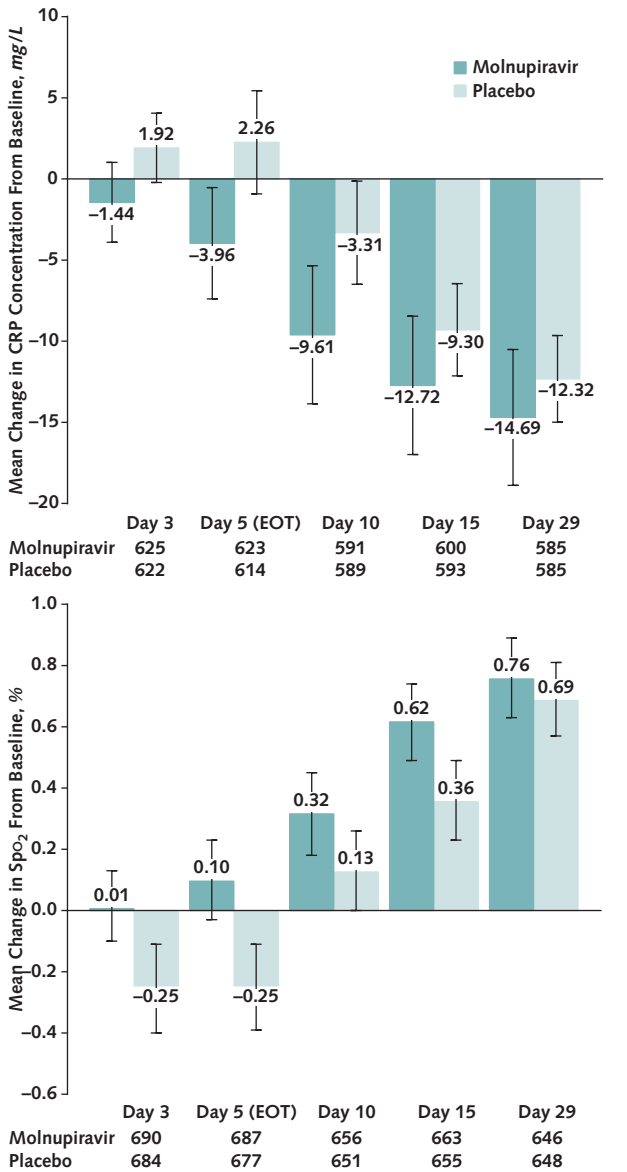
In the phase 3 component of MOVe-OUT, 1433 participants were randomly assigned from 107 sites in Africa, the Asia-Pacific region, Europe, Latin America, and North America. Of these, 710 molnupiravir-treated participants and 701 placebo recipients were included in the safety population. One participant in the molnupiravir group and 2 in the placebo group were hospitalized before receiving the first dose of study drug and were excluded from the MITT population (**Appendix Figure**, available at Annals.org). Baseline demographic and clinical characteristics were generally similar between groups (**Table**). One hundred fifty-two participants in the molnupiravir group and 151 in the placebo group received systemic corticosteroids before or during the study treatment period in the safety population. Forty-eight of 709 (6.8%) molnupiravir-treated participants and 67 of 699 (9.6%) placebo recipients in the MITT population were hospitalized through day 29.

In the safety population, participants who received molnupiravir had earlier and larger reductions in mean change from baseline in CRP values at all postbaseline visits than those who received placebo. In the molnupiravir group, a reduction in mean CRP values was evident as early as day 3 (the first postbaseline visit) and continued through day 29, whereas in the placebo group, a reduction was not seen until day 10 (**Figure 1**, *top*; **Appendix Table 3**, available at Annals.org).

Similarly, molnupiravir-treated participants had earlier and larger improvements in mean change from baseline in Spo_2 values compared with placebo recipients at all postbaseline visits in the safety population. Improvement in mean Spo_2 was observed as early as day 3 and continued through day 29 in the molnupiravir group, whereas placebo recipients did not show an increase in mean Spo_2 until day 10 (**Figure 1**, *bottom*; **Appendix Table 3**).

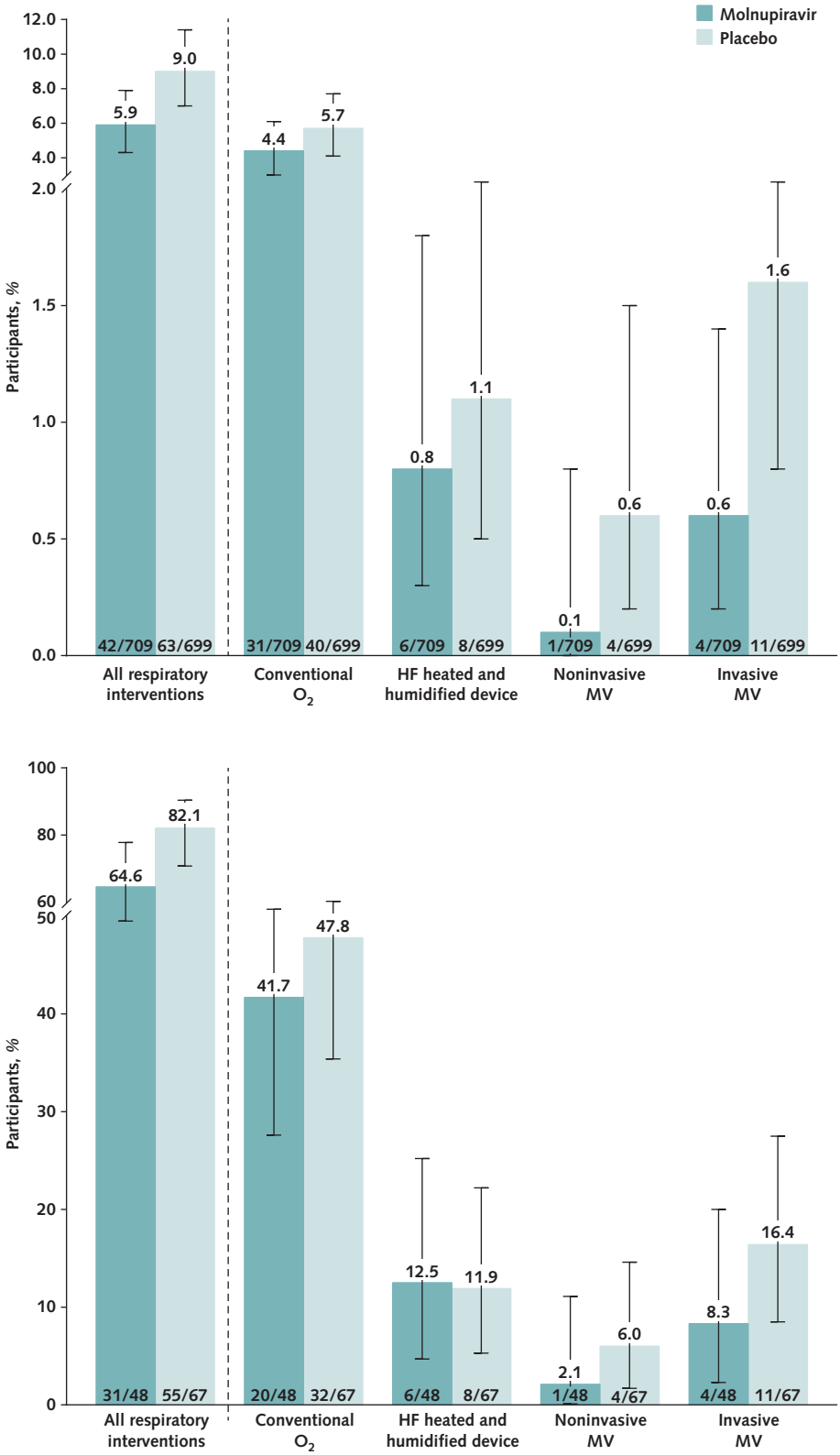
In the MITT population, fewer molnupiravir-treated participants required use of respiratory interventions (**Figure 2**, *top*), with an RRR of 34.3% (CI, 4.3% to 54.9%) for all respiratory interventions compared with placebo recipients. The RRRs were 23.6% (CI, −20.7% to 51.6%) for oxygen therapy with conventional oxygen, 26.1% (CI, −112% to 74.2%) for a high-flow heated and humidified device, 75.4% (CI, −120% to 97.2%) for noninvasive mechanical ventilation, and 64.1% (CI, −12.1% to 88.5%) for invasive mechanical ventilation. A reduction in the use of respiratory interventions was also observed in the subgroup of participants who required hospitalization after randomization (**Figure 2**, *bottom*). Compared with placebo recipients, this subgroup had RRRs of 21.3% (CI, 0.2% to 38.0%) for all respiratory interventions, 12.8% (CI, −32.5% to 42.6%) for conventional oxygen, −4.7% (CI, −182.2% to 61.2%) for a high-flow heated and

Figure 1. Mean change in CRP concentration (*top*) and Spo_2 (*bottom*) through day 29 (safety population).



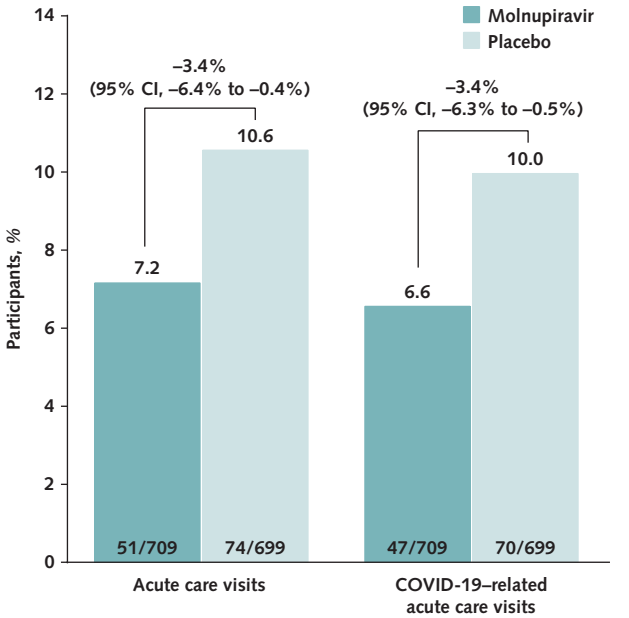
Error bars represent 95% CIs. CRP = high-sensitivity C-reactive protein; EOT = end of therapy; Spo_2 = oxygen saturation.

Figure 2. Respiratory interventions through day 29 in the MITT population (*top*) and the hospitalized MITT population (*bottom*).



Error bars represent 95% CIs. Each participant was counted only once according to the highest level of O_2 therapy needed. Respiratory interventions included conventional O_2, HF heated and humidified device, noninvasive MV, and invasive MV. HF = high-flow; MITT = modified intention-to-treat; MV = mechanical ventilation; O_2 = oxygen.

Figure 3. Acute care visits and COVID-19–related acute care visits through day 29 (MITT population).



95% CIs were based on the Miettinen-Nurminen method, with stratification by randomization strata. MITT = modified intention-to-treat.

humidified device, 65.1% (CI, −202.5% to 96.0%) for noninvasive mechanical ventilation, and 49.2% (CI, −49.9% to 82.8%) for invasive mechanical ventilation. In this subgroup of hospitalized participants, the median time to hospital discharge was 9 days (CI, 7 to 12 days) in the molnupiravir group and 12 days (CI, 9 to 14 days) in the placebo group.

In the MITT population, prespecified analyses showed that the proportion of participants who had an acute care visit or a COVID-19–related acute care visit was lower in the molnupiravir group (7.2% and 6.6%, respectively) than in the placebo group (10.6% and 10.0%, respectively) (**Figure 3**), with RRRs of 32.1% (CI, 4.4% to 51.7%) and 33.8% (CI, 5.6% to 53.6%), respectively.

DISCUSSION

In the phase 3 portion of the MOVe-OUT trial, participants receiving molnupiravir showed faster normalization of CRP and Spo_2 than placebo recipients. The improvements in these clinically relevant surrogate markers were noted early in the 5-day treatment period and continued through day 29. Molnupiravir-treated participants required fewer respiratory interventions, including invasive mechanical ventilation, than those receiving placebo. Even among the subgroup of hospitalized participants, molnupiravir was associated with a reduced need for any respiratory intervention as well as invasive mechanical ventilation. Furthermore, hospitalized participants who received molnupiravir were discharged earlier than those who received placebo. Finally, the need for acute care visits and COVID-19–related acute care visits was lower with molnupiravir versus placebo.

Excessive inflammation and respiratory decompensation are key drivers of COVID-19 progression, morbidity, and mortality (44–48). Higher CRP concentrations are associated with severe or critical illness, respiratory failure, and mortality in patients with COVID-19 (46–49), and CRP decreases as patients recover from SARS-CoV-2 infection (46, 49–52). Spo_2 can be easily and continuously measured with pulse oximetry, allowing providers to monitor respiratory function in patients with COVID-19 not only in acute care settings but also at home. The continuous decreases in CRP concentration and increases in Spo_2 with molnupiravir indicate subsiding systemic inflammation and recovering respiratory function. This correlates with the decreased need for respiratory interventions (including invasive mechanical ventilation) and acute care visits (including COVID-19–related acute care visits) and the shorter hospital stays in participants who received molnupiravir. The decreased need for invasive mechanical ventilation is particularly relevant because patients with COVID-19 who receive this respiratory intervention have mortality rates up to 50% (53–55).

Over the course of the pandemic, medical facilities have had to pause or limit routine, nonessential medical services and reallocate health care resources, including personal protective equipment, ventilators, and medications, to sustain the capacity to manage both patients with COVID-19 and those with other conditions requiring hospital care (5, 6, 8). Given that health care systems continue to be overburdened (7, 56), decreasing the need for invasive mechanical ventilation, the need for acute care visits, and the time to hospital discharge are particularly important to preserve limited health care resources. Participants treated with molnupiravir demonstrated earlier clinical improvement (shown by improvement in CRP concentration and Spo_2 on day 3) than placebo recipients, with a shorter length of stay in participants who were hospitalized, providing a possible opportunity for more efficient use of hospital beds.

A strength of this work is that MOVe-OUT is a large, global, prospective, double-blind, placebo-controlled trial that allowed for a carefully controlled evaluation of CRP and Spo_2 over time. We were able to objectively evaluate clinical improvement with these surrogate markers. An additional strength of this analysis was the prespecified evaluation of acute care visits, which included inpatient hospitalizations. This allowed us to include medically attended visits not captured strictly by hospitalizations. Ongoing real-world research will yield additional evidence on the use of molnupiravir therapy in the outpatient setting (57).

A key limitation of this work is that although the data were collected prospectively, most of these analyses were conducted retrospectively. In addition, although these analyses elucidate the immediate and shorter-term benefits of molnupiravir therapy for patients with COVID-19, potential longer-term benefits of molnupiravir therapy on postacute sequelae of COVID-19 were not studied in this trial. Another limitation is that participants in MOVe-OUT were not immunized against SARS-CoV-2; it is unclear whether vaccination or the time elapsed since vaccination would affect these findings. Finally, the potential financial impact associated with the observed decreases in respiratory

interventions and medical services with molnupiravir was not included in this analysis; the cost-effectiveness of molnupiravir therapy has been evaluated separately (58).

Altogether, these findings suggest there is added clinical value of molnupiravir for the treatment of nonhospitalized adults with mild to moderate COVID-19. Meaningful benefits of molnupiravir to patients and health care systems may exceed the previously demonstrated benefits of reducing hospitalizations or death due to disease progression as well as alleviating symptoms in high-risk patients.

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Data Sharing Statement: The following data will be made available with publication: deidentified participant data and clinical study reports. (The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via e-mail to dataaccess@merck.com.) No supporting documents will be made available. The data will be made available to qualified scientific researchers for specific purposes outlined in a proposal after the researcher enters into a standard data sharing agreement and the proposal is approved. Researchers must commit to transparency in publication.

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Appendix Table 1. COVID-19 Disease Severity Definitions

Disease Severity	Definition
Mild COVID-19	Laboratory-confirmed SARS-CoV-2 infection and ≥1 of the following signs or symptoms: fever >38 °C, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell and both of the following: • Respiratory rate <20 breaths/min • Heart rate <90 beats/min and either of the following • Spo_2 >93% on room air • Receipt of supplemental oxygen for a reason other than COVID-19, with no increase since onset of COVID-19 signs or symptoms and both of the following: • No shortness of breath at rest or with exertion • No respiratory failure, shock, or multiorgan dysfunction or failure
Moderate COVID-19	Laboratory-confirmed SARS-CoV-2 infection and ≥1 of the following signs or symptoms: fever >38 °C, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell and ≥1 of the following: • Respiratory rate ≥20 to <30 breaths/min • Heart rate ≥90 to <125 beats/min • Shortness of breath with exertion and any of the following: • Spo_2 >93% on room air • Receipt of supplemental oxygen for a reason other than COVID-19, with no increase since onset of COVID-19 signs or symptoms • Receipt of ≤4 L of supplemental oxygen per minute for COVID-19, but not previously receiving supplemental oxygen, regardless of Spo_2 and both of the following: • No shortness of breath at rest • No respiratory failure, shock, or multiorgan dysfunction or failure

Spo_2 = oxygen saturation.

Appendix Table 2. Acute Care Visit and Hospitalization Definitions

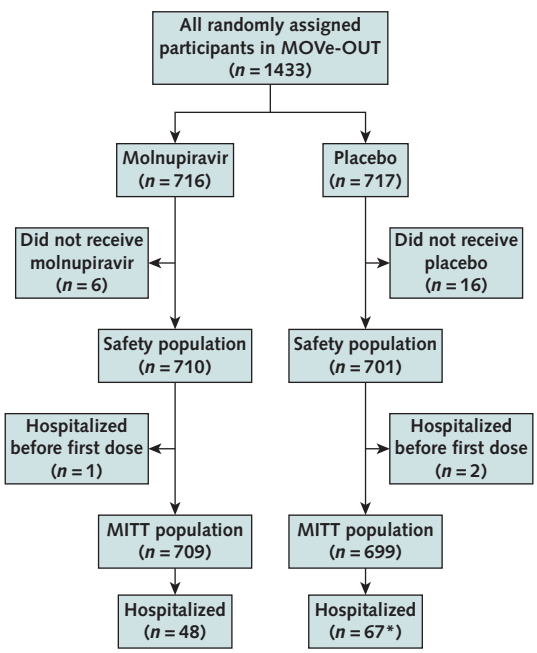
Event	Definition
Acute care visit	Any amount of time Hospital or similar acute care facility • Emergency department • Facility created to address hospitalization during the COVID-19 pandemic Urgent care Office or clinic visit with a health care provider Home visit by a health care provider
Hospitalization	≥24 hours Hospital or similar acute care facility • Emergency department • Facility created to address hospitalization during the COVID-19 pandemic

Appendix Table 3. Mean CRP Concentrations and Spo_2 Through Day 29 in the Safety Population

Variable	Molnupiravir			Placebo		
	Participants, *n*	Mean Value (95% CI)		Participants, *n*	Mean Value (95% CI)	
		At Baseline	At Postbaseline Time Point		At Baseline	At Postbaseline Time Point
CRP concentration, *mg/L*						
Day 1 (baseline)	662	21.23 (17.28–25.18)	–	652	18.02 (15.47–20.56)	–
Day 3	625	20.18 (16.20–24.17)	18.75 (15.58–21.92)	622	17.36 (14.83–19.89)	19.28 (16.23–22.33)
Day 5 (EOT)	623	19.30 (15.37–23.23)	15.34 (12.83–17.85)	614	16.96 (14.47–19.45)	19.22 (16.18–22.26)
Day 10	591	19.46 (15.42–23.49)	9.85 (8.00–11.69)	589	16.40 (13.88–18.91)	13.09 (10.74–15.44)
Day 15	600	20.19 (16.07–24.31)	7.47 (5.63–9.31)	593	16.82 (14.23–19.41)	7.52 (5.84–9.20)
Day 29	585	20.45 (16.30–24.60)	5.76 (4.72–6.80)	585	17.16 (14.54–19.78)	4.85 (3.99–5.70)
Spo_2, %						
Day 1 (baseline)	710	96.72 (96.60–96.84)	–	701	96.91 (96.80–97.02)	–
Day 3	690	96.75 (96.63–96.87)	96.76 (96.62–96.90)	684	96.89 (96.78–97.01)	96.64 (96.47–96.81)
Day 5 (EOT)	687	96.74 (96.63–96.86)	96.84 (96.69–96.99)	677	96.92 (96.81–97.03)	96.67 (96.51–96.83)
Day 10	656	96.76 (96.64–96.88)	97.08 (96.94–97.22)	651	96.91 (96.80–97.03)	97.04 (96.90–97.18)
Day 15	663	96.75 (96.63–96.87)	97.37 (97.25–97.49)	655	96.91 (96.79–97.02)	97.27 (97.14–97.40)
Day 29	646	96.77 (96.65–96.89)	97.53 (97.41–97.65)	648	96.91 (96.79–97.02)	97.60 (97.49–97.71)

CRP = high-sensitivity C-reactive protein; EOT = end of therapy; Spo_2 = oxygen saturation.

Appendix Figure. Participant flow chart.



MITT = modified intention-to-treat.
* One placebo recipient was lost to follow-up and was thus not considered to be hospitalized for this analysis.