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ORIGINAL ARTICLE

Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19

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Abstract

BACKGROUND Molnupiravir is an oral prodrug of β-D-N4-hydroxycytidine, active against SARS-CoV-2 in vitro and in animal models. We report data from the phase 2 component of MOVe-IN, a clinical trial evaluating molnupiravir in patients hospitalized with Covid-19.

METHODS We conducted a randomized, placebo-controlled, double-blind phase 2/3 trial in patients 18 years old and older requiring in-hospital treatment for laboratory-confirmed Covid-19 with symptom onset 10 or fewer days before randomization. Participants were randomly assigned to placebo or molnupiravir 200 mg, 400 mg, or 800 mg (1:1:1:1 ratio), twice daily for 5 days. Primary end points were safety and sustained recovery (participant alive and either not hospitalized or medically ready for discharge) through day 29.

RESULTS Of 304 randomly assigned participants, 218 received at least one dose of molnupiravir and 75 of placebo. At baseline, 74.0% had at least one risk factor for severe Covid-19. Adverse events were reported in 121 of 218 (55.5%) molnupiravir-treated and 46 of 75 (61.3%) placebo-treated participants, with no apparent dose effect on adverse event rates and no evidence of hematologic toxicity based on prespecified adverse events. Of 16 confirmed deaths, most were in participants with severe Covid-19 (75.0%), with underlying comorbidities (87.5%), older than 60 years of age (81.3%), and/or symptom duration longer than 5 days (75.0%) at randomization. Median time to sustained recovery was 9 days in all groups, with similar day 29 recovery rates ranging from 81.5% to 85.2%.

CONCLUSIONS In this phase 2 trial of patients hospitalized with Covid-19, a 5-day course of molnupiravir up to 800 mg twice daily was not associated with dose-limiting

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side effects or adverse events, but did not demonstrate clinical benefit. (Funded by Merck Sharp & Dohme; ClinicalTrials.gov NCT04575584.)

Introduction

There is a need for safe, effective, and easily administered antiviral therapies to treat patients hospitalized for Covid-19; such treatments should accelerate recovery times and reduce mortality. Molnupiravir is an orally administered, small-molecule ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC), which has submicromolar potency against ribonucleic acid (RNA) respiratory viruses, including SARS-CoV-2.[1–4] Molnupiravir is rapidly absorbed and converted into NHC, which is distributed systemically and phosphorylated intracellularly to NHC-triphosphate (NHC-TP).[5] NHC-TP is incorporated into the viral genome, which increases mismatch error rates during viral RNA replication. Once a tolerated threshold of viral RNA errors has been exceeded, inhibition of viral replication and production of noninfectious virus lead to viral extinction.[1,3,6] In an animal model, molnupiravir retained full efficacy against SARS-CoV-2 variants of concern.[7] The favorable safety and tolerability profile of molnupiravir seen in preclinical studies and a phase 1 trial provided the needed equipoise for further clinical development.[5,8]

The potential of molnupiravir as an antiviral treatment for Covid-19 is being evaluated in two phase 2/3 studies, one in outpatients (MOVe-OUT trial[9,10]) and the other in hospitalized patients (MOVe-IN trial). In this study, we report safety, efficacy, pharmacokinetic, and virology data from the recently completed phase 2, dose-finding component of MOVe-IN.

Methods

TRIAL DESIGN AND PARTICIPANTS

MOVe-IN (protocol MK-4482-001) was a randomized, placebo-controlled, double-blind phase 2/3 trial evaluating safety and efficacy of molnupiravir in hospitalized adults with Covid-19 (ClinicalTrials.gov NCT04575584). The phase 2 component of MOVe-IN (initiated October 21, 2020) was conducted at 65 hospitals/treatment centers in 15 countries globally (Table S1 in the Supplementary Appendix). The trial enrolled adult patients requiring in-hospital treatment for laboratory-confirmed Covid-19 with sign/symptom onset 10 or fewer days before randomization. Key exclusion criteria were critical illness due to Covid-19 (i.e., respiratory failure [defined as need for invasive or noninvasive mechanical ventilation, oxygen delivered by high-flow nasal cannula, or extracorporeal membrane oxygenation], shock, or multiorgan dysfunction/failure), severely immunocompromised persons who are not expected to have a Covid-19 disease course and/or clinical response to study treatment typical of the general population, low platelet count (<100,000/μl or platelet transfusion ≤5 days prior), and SARS-CoV-2 vaccination. Standard-of-care treatment with remdesivir and/or glucocorticoids was permitted, but other immunomodulators (including interleukin-6 inhibitors and kinase inhibitors) were prohibited for purposes of Covid-19 treatment.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards/ethics committees and regulatory agencies. Written informed consent was obtained from all participants. Full details of the trial can be found in the protocol available online. The trial was designed by sponsor (Merck & Co., Inc., Kenilworth, NJ) representatives. Safety oversight was performed by an independent data monitoring committee. Data were collected by investigators and site personnel, analyzed by sponsor statisticians, and interpreted by the authors. The first draft of the manuscript was written with assistance of a medical writer who is a sponsor employee, based on author guidance. All authors reviewed and edited subsequent versions, approved the submitted version, and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol, which is available with the full text of this article at evidence.NEJM.org.

RANDOMIZATION AND INTERVENTIONS

Eligible participants were randomly assigned, via a centralized intervention randomization system, 1:1:1:1 to placebo or molnupiravir 200 mg, 400 mg, or 800 mg, administered twice daily orally (or by an alternative route such as via nasogastric tube, for participants unable to swallow study intervention capsules) for 5 days. Randomization was stratified (block size: 4, the minimum block size for a 4-arm trial) by time from sign/symptom onset to randomization (≤5 days or >5 days), age (≤60 years and >60 years), and remdesivir use for the index Covid-19

infection before and/or at randomization (yes or no). Participants, investigators, and study staff (except unblinded site pharmacists) remained blinded to allocation assignment until study completion.

PROCEDURES

Covid-19 signs/symptoms and oxygenation status were assessed daily during treatment and at days 10 (±1), 15 (+3), and 29 (+3). Nasopharyngeal swabs for virology analyses were collected on days 1, 3, 5 (end of treatment visit), 10 (±1), 15 (+3), and 29 (+3). Adverse events were collected during treatment and for 14 days following end of treatment. Investigators were advised to use open-ended, nonleading verbal questioning of participants to inquire about the occurrence of adverse events. Venous blood samples for pharmacokinetic analyses were collected predose and 1, 3, 5, and 8 hours after the 9th or 10th dose of study intervention.

OUTCOME MEASURES

The co-primary end points were safety and sustained recovery. Safety was evaluated as rates of adverse events reported during the safety follow-up period (from randomization through 14 days after end of treatment) in the safety population, which comprised all participants who received at least one dose of study intervention. Adverse events leading to discontinuation of study intervention reported during the safety follow-up period and adverse events leading to death were also recorded, including all deaths that occurred after the safety follow-up period and were the result of an adverse event that began during the safety follow-up period. Sustained recovery was defined as participants being alive and either not hospitalized (i.e., discharged from the hospital, not rehospitalized or transferred to another hospital, and not discharged to hospice care) or medically ready for hospital discharge (i.e., does not require ongoing medical care but remains in the hospital for infection control or nonmedical reasons) through day 29, analyzed in the modified intent-to-treat population (all participants with one or more doses of study intervention). Incidence of platelet levels <50,000/μl (confirmed by repeat testing) after initiating study intervention was evaluated as a prespecified event potentially indicating hematologic toxicity. Secondary efficacy end points included day 29 all-cause mortality; World Health Organization (WHO) Clinical Progression Scale (11-point ordinal scale for clinical progression, ranging from 0, "uninfected; no viral RNA detected," to 10, "dead"); Pulmonary Score (7-point ordinal scale that focuses on the respiratory sequelae of Covid-19 based on oxygen requirements, ranging from 1, "minimal or no symptoms," to 7, "death"); Pulmonary+ Score (7-point ordinal scale that focuses on Covid-19 disease severity, ranging from 1, "minimal or no symptoms," to 7, "death"); and the National Early Warning Score (21-point ordinal aggregate score ranging from 0 through 20, where an aggregate score of ≤4 indicates a need for prompt assessment by a registered nurse, aggregate scores of 5 or 6 [or any single parameter score of 3] indicate a need for urgent clinical review, and an aggregate score of 7 indicates a need for emergency clinical review).

Molnupiravir's longitudinal impact on SARS-CoV-2 viral load from nasopharyngeal samples was assessed through real-time polymerase chain reaction (PCR). To evaluate molnupiravir's effect on viral RNA error rates, nasopharyngeal samples containing >22,000 copies/ml of SARS-CoV-2 RNA underwent complete genome next-generation sequencing using the Ion AmpliSeq SARS-CoV-2 research assay (Thermo Fisher Scientific, Waltham, MA) on an Ion Torrent Genexus integrated sequencer (Thermo Fisher Scientific). Viral RNA error rates were calculated by determining the number of nucleotide changes (per 10,000 nucleotides, with an allele frequency ≥2%) observed across the entire genome at days 3 and 5 compared with baseline. Plasma NHC and intracellular (from peripheral blood mononuclear cells) NHC-TP levels were determined. Plasma NHC peak concentrations (C_{max}) and area under the curve $(AUC)_{0\text{-}12}$ were estimated from a preliminary population pharmacokinetics model built using pooled phase 1 and 2 data.[5]

STATISTICAL ANALYSIS

The co-primary end point of safety was analyzed descriptively. Of note, mortality was reported and analyzed differently for this safety analysis than for the efficacy analyses. The safety analyses included all observed deaths resulting from an adverse event (many of which were associated with Covid-19) that began during the safety follow-up period regardless of the timing of the death. For the secondary end point of day 29 all-cause mortality, all deaths occurring through day 29 were included, and participants with unknown survival status by day 29 were imputed as dead; unlike the safety analysis, deaths that occurred after day 29 were excluded.

Median time to recovery and sustained recovery rates for each group, with 95% confidence intervals, were determined using the Kaplan-Meier method. Missing data for

the co-primary end point of sustained recovery were handled through data censoring based on the following assumptions: failure to recover and/or death were both censored at day 29; recovery followed by subsequent loss to follow up before day 29 was censored at the day of loss to follow-up; or withdrawal (i.e., discontinuation from the study for reasons other than death or loss to follow-up) before day 29 was censored at the day of discontinuation. Hazard ratios comparing sustained recovery rates between molnupiravir and placebo were estimated from a Cox regression model.

The phase 2 component was not designed for hypothesis testing; sample sizes were primarily selected to support pharmacokinetic/pharmacodynamic modeling for dose selection. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

PARTICIPANTS

Of 304 participants randomly assigned (Table S2) between October 19, 2020 and January 12, 2021, 218 and 75 received one or more doses of molnupiravir or placebo, respectively. Of these modified intent-to-treat participants, 277 (94.5%) completed 5 days of study intervention and 258 (88.1%) finished the study through day 29 (Fig. 1).

Key baseline characteristics in each treatment group are shown in Table 1 (additional baseline data are provided in Tables S3 and S4). Most participants (76.3%) had more than 5 days from sign/symptom onset to randomization (mean duration 7.1 days); only 8.2% had Covid-19 sign/symptom duration of 72 hours or less before randomization (Table S5). More than half, 67.1%, also received glucocorticoids before/at randomization, 76.3% did not receive remdesivir before/at randomization, and 74.0% had one or more risk factors for severe Covid-19 (most frequent were age >60 years [41.1%] and obesity [40.1%]). Overall, 31.9% had confirmed SARS-CoV-2 nucleocapsid antibodies at baseline. Positive SARS-CoV-2 nucleocapsid antibody tests were reported for 37.9% of participants who had enrolled in the trial more than 5 days from sign/symptom onset compared with 12.7% of participants enrolled 5 or fewer days from sign/symptom onset. Severe Covid-19 at baseline was most frequent (53.9%) in the molnupiravir 800 mg group; slightly more participants receiving molnupiravir 800 mg (77.6%) and 400 mg (77.3%) had risk factors for severe illness than those receiving molnupiravir 200 mg (69.3%) or placebo (71.8%). Glucocorticoid use was 65.0% overall in the molnupiravir groups and 73.1% in the placebo group.

SAFETY

Rates of adverse events and serious adverse events were comparable across treatment groups, with no apparent molnupiravir dose effect (Table 2). Adverse events were reported in 121 of 218 (55.5%) molnupiravir-treated and 46 of 75 (61.3%) placebo-treated participants. As expected, many reported adverse events are also common in patients with Covid-19 not receiving active treatment (and also outside the clinical trial setting), making it difficult to determine whether an adverse event was caused by molnupiravir (Tables S6 and S7); however, there were no differences between treatment groups in rates of adverse events potentially associated with Covid-19, such as thromboembolic events. Thrombocytopenia (defined in this study as <50,000 platelets/μl) after initiation of study intervention was not reported with molnupiravir. Abnormal laboratory test results were more frequently reported with placebo. Only one participant discontinued study intervention due to an adverse event (respiratory failure, in the molnupiravir 400 mg group), which was serious and reported as resolved after approximately 2 months. Adverse event rates across all groups, active and placebo, were generally similar between participants with and without prior/concomitant glucocorticoids; serious adverse events appeared to be more frequent in participants with prior/concomitant glucocorticoid use (Table S8).

Due to the differences in analysis approaches and criteria for inclusion of observed events (see Methods), the number of deaths reported in the safety analysis differ from those in the all-cause mortality analysis (Fig. S2). Of the 16 adverse events resulting in death, 14 occurred in participants treated with molnupiravir (SARS-CoV-2 nucleocapsid antibody status: 7 negative, 3 positive, and 4 unknown) and 2 with placebo (SARS-CoV-2 nucleocapsid antibody status: 1 negative and 1 positive). Of note, 4 of these 16 deaths (3 molnupiravir and 1 placebo) happened after day 29. Most of the deaths in the safety analysis occurred in participants with underlying comorbidities (12 molnupiravir and 2 placebo), those older than 60 years old (11 molnupiravir and 2 placebo), those with severe Covid-19 at baseline (10 molnupiravir and 2 placebo), and those with sign/symptom duration more than 5 days before

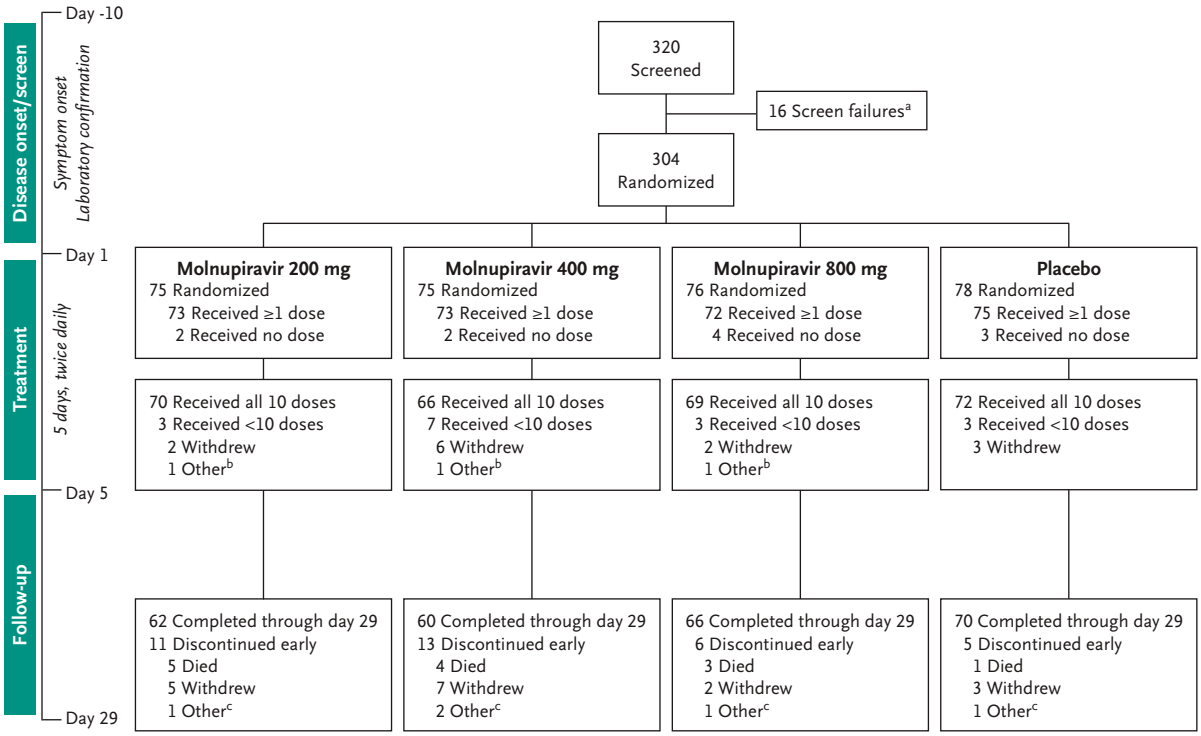

Figure 1. Study Design and Enrollment.

[a]Of the 16 participants who were not randomly assigned following initial screening for study eligibility, 2 declined to participate, 13 did not meet eligibility criteria, and 1 had other reasons. [b]Specific reasons for early discontinuation of study drug before receiving all 10 doses are not shown to prevent premature unblinding. Of the total three participants who discontinued study treatment early due to reasons other than withdrawing from the study on their own accord, one each discontinued study treatment early due to either an adverse event, loss to follow-up, or noncompliance with study drug. [c]Specific reasons for study discontinuation before a participant reached day 29 are not shown to prevent premature unblinding. Of the total five participants who discontinued the study due to reasons other than death or withdrawing from the study on their own accord, four were lost to follow-up and one was withdrawn by the investigator.

randomization (10 molnupiravir and 2 placebo). The most common adverse event resulting in death was "Covid-19" (reported for 6 of 16 participants), and most deaths were associated with complications of Covid-19 (including pneumonia, sepsis, or respiratory failure) or secondary bacterial infections (Table S9). Adverse events assessed as drug-related by the investigator in the safety population are listed in Table S7.

EFFICACY

Median time to sustained recovery was 9 days in all groups, with similar day 29 recovery rates ranging from 81.5 to 85.2% (Table 3). Post hoc analyses (some involving small subgroups) in participants older than 60 years old, without remdesivir or glucocorticoid use at or before randomization, with a negative SARS-CoV-2 baseline antibody test, and with 5 or fewer days from sign/symptom onset also showed no signal of a treatment effect (Table 3 and Table S10).

There was no evidence for a difference in all-cause mortality rates (ranging from 1.3% to 6.8%) through day 29 (Table 3). Of note, 2 of 14 deaths by day 29 were imputed because the survival status at day 29 of 1 participant treated with molnupiravir 400 mg and 1 with 800 mg was unknown (Fig. S2). There were no differences in the WHO Clinical Progression Scale (Table S11), Pulmonary (Table S12) and Pulmonary+ ordinal outcomes (Table S13), and National Early Warning Score (Table S14).

VIROLOGY

Next-generation sequencing showed that SARS-CoV-2 viral RNA error rates measured after treatment were generally higher with molnupiravir (especially the 800-mg

Table 1. Participant Baseline Demographics and Clinical Characteristics nasopharyngeal

Characteristic	Molnupiravir 200 mg (N=75)	Molnupiravir 400 mg (N=75)	Molnupiravir 800 mg (N=76)	Molnupiravir Combined (N=226)	Placebo (N=78)
Sex, female — no. (%)	32 (42.7)	34 (45.3)	32 (42.1)	98 (43.4)	34 (43.6)
Age, mean (SD)	56.9 (14.2)	57.0 (14.0)	56.8 (13.7)	56.9 (13.9)	57.1 (14.2)
>60 years of age — no. (%)	31 (41.3)	30 (40.0)	32 (42.1)	93 (41.2)	33 (42.3)
Race — no. (%)					
Native American	0 (0.0)	3 (4.0)	1 (1.3)	4 (1.8)	2 (2.6)
Asian	10 (13.3)	8 (10.7)	4 (5.3)	22 (9.7)	1 (1.3)
Black/African American	1 (1.3)	4 (5.3)	6 (7.9)	11 (4.9)	7 (9.0)
Pacific Islander	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)	0 (0.0)
White	58 (77.3)	52 (69.3)	54 (71.1)	164 (72.6)	63 (80.8)
Multiple	6 (8.0)	7 (9.3)	9 (11.8)	22 (9.7)	5 (6.4)
Unknown	0 (0.0)	1 (1.3)	1 (1.3)	2 (0.9)	0 (0.0)
Region — no. (%)					
North America	10 (13.3)	9 (12.0)	14 (18.4)	33 (14.6)	13 (16.7)
Latin America	19 (25.3)	25 (33.3)	21 (27.6)	65 (28.8)	21 (26.9)
Europe, Middle East, Africa	39 (52.0)	37 (49.3)	40 (52.6)	116 (51.3)	43 (55.1)
Asia Pacific	7 (9.3)	4 (5.3)	1 (1.3)	12 (5.3)	1 (1.3)
Time from sign/symptom onset to randomization, mean (SD) — no. (%)	7.0 (2.2)	7.3 (2.1)	7.1 (2.3)	7.1 (2.2)	6.9 (2.2)
≤5 days	18 (24.0)	15 (20.0)	18 (23.7)	51 (22.6)	20 (25.6)
>5 days	57 (76.0)	60 (80.0)	58 (76.3)	175 (77.4)	57 (73.1)
Remdesivir prior to/at randomization — no. (%)	16 (21.3)	17 (22.7)	19 (25.0)	52 (23.0)	20 (25.6)
Systemic glucocorticoid prior to/at randomization — no. (%)*	44 (58.7)	50 (66.7)	53 (69.7)	147 (65.0)	57 (73.1)
Severity of Covid-19 — no. (%)†					
Mild	15 (20.0)	9 (12.0)	8 (10.5)	32 (14.2)	9 (11.5)
Moderate	36 (48.0)	32 (42.7)	27 (35.5)	95 (42.0)	36 (46.2)
Severe	24 (32.0)	34 (45.3)	41 (53.9)	99 (43.8)	33 (42.3)
SARS-CoV-2 nasopharyngeal RNA — no. (%)‡					
Detectable	69 (92.0)	69 (92.0)	63 (82.9)	201 (88.9)	65 (83.3)
Undetectable	2 (2.7)	2 (2.7)	5 (6.6)	9 (4.0)	6 (7.7)
Unknown	4 (5.3)	4 (5.3)	8 (10.5)	16 (7.1)	7 (9.0)
SARS-CoV-2 nucleocapsid antibody — no. (%)§					
Positive	26 (34.7)	19 (25.3)	24 (31.6)	69 (30.5)	28 (35.9)
Negative	29 (38.7)	36 (48.0)	32 (42.1)	97 (42.9)	30 (38.5)
Unknown	20 (26.7)	20 (26.7)	20 (26.3)	60 (26.5)	20 (25.6)
Risk factors for severe Covid-19¶ — no. (%)					
At least one risk factor	52 (69.3)	58 (77.3)	59 (77.6)	169 (74.8)	56 (71.8)

(continued)

Table 1. Participant Baseline Demographics and Clinical Characteristics nasopharyngeal (cont.)					
Characteristic	Molnupiravir 200 mg (N=75)	Molnupiravir 400 mg (N=75)	Molnupiravir 800 mg (N=76)	Molnupiravir Combined (N=226)	Placebo (N=78)
Two or more risk factors	26 (34.7)	29 (38.7)	28 (36.8)	83 (36.7)	24 (30.8)

Data provided for all randomized participants. Race was self-reported by participants according to a set of available options.

* Intravenous, intramuscular, or oral glucocorticoids, mostly dexamethasone. In the modified intent-to-treat population, the corresponding numbers were 44 of 73 (60.3%) for molnupiravir 200 mg, 50 of 73 (68.5%) for molnupiravir 400 mg, 52 of 72 (72.2%) for molnupiravir 800 mg, 146 of 218 (67.0%) for molnupiravir combined, and 56 of 75 (74.7%) for placebo.

† Definitions for disease severity were adapted from COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry,[11] WHO COVID-19 case definition,[12] and Tenforde et al.[13]

‡ SARS-CoV-2 RNA real-time PCR assay.

§ Positive SARS-CoV-2 antibody tests (Roche Elecsys Anti-SARS-CoV-2 total nucleocapsid antibody assay; cutoff index <1.0 deemed negative, and cutoff index ≥1.0 deemed positive) were reported for 37.9% of participants who had enrolled in the trial more than 5 days from sign/symptom onset compared to 12.7% of participants enrolled 5 or fewer days from sign/symptom onset. This antibody test does not allow conclusions about vaccination status (which was an exclusion criterion for this trial) but indicates recent/ongoing or prior infection with SARS-CoV-2.

¶ The following risk factors were evaluated, based on medical history and any other clinical information available to the investigator at screening: older than 60 years of age, active cancer (other than minor cancers not associated with immunosuppression or significant morbidity/mortality [e.g., basal cell carcinomas]), chronic kidney disease (excluding participants requiring dialysis or with an estimated glomerular filtration rate of less than 30 ml/min/1.73 m^2), chronic obstructive pulmonary disease, immunocompromised/solid-organ transplant recipient, obesity (body mass index 30 kg/m^2 or higher), serious heart conditions (congestive cardiac failure, coronary artery disease, and/or cardiomyopathies), diabetes mellitus, and sickle cell disease.

dose) than placebo (Table S15). At end of treatment, mean error rates per 10,000 nucleotides with an allele frequency 2% or higher were 5.9 with 800 mg molnupiravir compared with 2.8 for placebo, consistent with molnupiravir's mechanism of action. The proportion of participants with undetectable SARS-CoV-2 RNA (Table S16) in each group over time is shown in Figure 2, both for the overall modified intent-to-treat population (Fig. 2A) and specifically for participants with 5 or fewer days since Covid-19 sign/symptom onset (Fig. 2B). There was no clear difference in SARS-CoV-2 RNA viral load reduction from baseline between molnupiravir and placebo (Table S17).

PHARMACOKINETICS

NHC plasma levels were available from 196 of 218 (89.9%) participants; 917 samples were collected. Model-estimated plasma NHC exposures ($AUC_{0\text{-}12}$) and peak plasma concentrations (C_{max}) after last dose increased proportionally with molnupiravir dose (Fig. S1). Observed and model-estimated NHC exposures and peak concentrations from these hospitalized patients with Covid-19 were similar to those seen in healthy volunteers (Fig. S2). Intracellular NHC-TP levels also demonstrated a dose-related increase and appeared to have a longer terminal half-life than NHC (data not shown).

Discussion

In this phase 2, dose-finding component of the phase 2/3 MOVe-IN trial in patients hospitalized for Covid-19, three molnupiravir dose levels (200 mg, 400 mg, and 800 mg) administered twice daily for 5 days were not associated with dose-limiting side effects up to the highest dose and had adverse event rates comparable to those reported for placebo. In the safety assessment period of this acute-care trial (5 days of treatment and 14 days of observation for adverse events, including any adverse events leading to death), no safety concerns with molnupiravir were identified, including no evidence of hematologic, pancreatic, or hepatic toxicity.

Many of the observed adverse events were associated with Covid-19. A higher number of adverse events leading to death were reported with molnupiravir than placebo. Most of these deaths occurred in participants who were older, had underlying comorbidities, and/or had severe Covid-19 at baseline, and most appeared to be associated with complications from Covid-19 (which was itself the most frequently reported adverse event term resulting in death). While the percentage of participants with adverse events leading to death was higher in each molnupiravir group compared with placebo, the number of deaths was small overall, and 95% confidence intervals for the differences all included zero. Furthermore, the overall mortality rate in MOVe-IN of about 5% was relatively low for a trial conducted in roughly similar patients hospitalized for treatment of Covid-19; two large analyses reported mortality rates of 12% and 26% among hospitalized, non–critically ill patients with Covid-19,[14,15] and a clinical trial with a study design comparable to ours reported mortality rates of 11% and 15% in hospitalized adults treated with remdesivir or

Table 2. Incidence of Adverse Events During Treatment and the Subsequent 14-Day Follow-up Period Regardless of Investigator-Assessed Causality					
Specific adverse event type — no. (%)	**Molnupiravir 200 mg (N=73)**	**Molnupiravir 400 mg (N=73)**	**Molnupiravir 800 mg (N=72)**	**Molnupiravir Combined (N=218)**	**Placebo (N=75)**
Any adverse event*	40 (54.8)	36 (49.3)	45 (62.5)	121 (55.5)	46 (61.3)
Blood and lymphatic system disorders	0 (0.0)	2 (2.7)	2 (2.8)	4 (1.8)	3 (4.0)
Cardiac disorders	1 (1.4)	3 (4.1)	1 (1.4)	5 (2.3)	3 (4.0)
Congenital, familial, and genetic disorders	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)	0 (0.0)
Eye disorders	1 (1.4)	0 (0.0)	1 (1.4)	2 (0.9)	0 (0.0)
Gastrointestinal disorders	13 (17.8)	5 (6.8)	10 (13.9)	28 (12.8)	10 (13.3)
General disorders and administration site conditions	2 (2.7)	3 (4.1)	2 (2.8)	7 (3.2)	1 (1.3)
Hepatobiliary disorders	2 (2.7)	2 (2.7)	2 (2.8)	6 (2.8)	2 (2.7)
Immune system disorders (seasonal allergy)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Infections and infestations	13 (17.8)	10 (13.7)	16 (22.2)	39 (17.9)	12 (16.0)
Injury, poisoning, and procedural complications	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)	1 (1.3)
Investigations	9 (12.3)	11 (15.1)	15 (20.8)	35 (16.1)	19 (25.3)
Metabolism and nutrition disorders	10 (13.7)	12 (16.4)	4 (5.6)	26 (11.9)	6 (8.0)
Musculoskeletal and connective tissue disorders	3 (4.1)	0 (0.0)	0 (0.0)	3 (1.4)	1 (1.3)
Neoplasms benign, malignant and unspecified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Nervous system disorders	3 (4.1)	2 (2.7)	1 (1.4)	6 (2.8)	3 (4.0)
Psychiatric disorders	4 (5.5)	1 (1.4)	3 (4.2)	8 (3.7)	4 (5.3)
Renal and urinary disorders	2 (2.7)	0 (0.0)	6 (8.3)	8 (3.7)	2 (2.7)
Respiratory, thoracic, and mediastinal disorders	8 (11.0)	7 (9.6)	9 (12.5)	24 (11.0)	11 (14.7)
Skin and subcutaneous tissue disorders	6 (8.2)	1 (1.4)	3 (4.2)	10 (4.6)	5 (6.7)
Vascular disorders	2 (2.7)	4 (5.5)	5 (6.9)	11 (5.0)	2 (2.7)
Any serious adverse event	11 (15.1)	9 (12.3)	13 (18.1)	33 (15.1)	12 (16.0)
Death†	6 (8.2)	4 (5.5)	4 (5.6)	14 (6.4)	2 (2.7)

Data provided for the safety population (i.e., all randomly assigned participants who received at least one dose of study treatment according to actual treatment received).

* Only one participant in this trial (in the molnupiravir 400 mg group) discontinued study intervention due to an adverse event (i.e., acute respiratory failure, reported as resolved after approximately 2 months, which was serious).

† A total of four deaths occurred after day 29 (n=1 placebo, n=2 molnupiravir 200 mg, and n=1 molnupiravir 800 mg), and although included in this adverse event analysis, are excluded from the mortality efficacy analysis.

placebo, respectively.[16] In line with other clinical trials, there were no apparent drug or dose effects on adverse event rates, including no clear impact on mortality.[5,9,10,17,18] As with any new drug, long-term toxicity can only be fully ascertained through ongoing pharmacovigilance.

We did not observe clinical efficacy of molnupiravir in the hospitalized participants studied: sustained recovery rates through day 29, the primary efficacy end point, were comparable across groups with identical median recovery times for all active and placebo groups. These results were consistent across analyzed subgroups, including participants who had not received treatment with remdesivir or glucocorticoids before or at randomization. Moreover, molnupiravir treatment did not impact secondary efficacy outcomes, including day 29 all-cause mortality; of note, mortality analyses were limited by unavailability of survival data from two participants who prematurely

Table 3. Rates of Sustained Recovery from Covid-19 and All-Cause Mortality Through Study Day 29

Characteristic	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
Sustained recovery* through day 29 (primary efficacy end point)				
Overall				
Number of participants	73	73	72	75
Recovery rate at day 29, % (95% CI)†	81.5 (71.4, 89.7)	85.2 (75.4, 92.6)	84.3 (74.8, 91.6)	84.7 (75.5, 91.9)
Recovery rate ratio vs. placebo (95% CI)‡	0.99 (0.68, 1.45)	1.13 (0.78, 1.65)	1.01 (0.69, 1.47)	—
Time since sign/symptom onset ≤5 days before randomization§				
Number of participants	17	14	16	19
Recovery rate at day 29, % (95% CI)†	74.9 (52.7, 92.2)	81.5 (55.3, 97.1)	93.8 (75.3, 99.6)	100.0 (—, —)
Recovery rate ratio vs. placebo (95% CI)¶	0.51 (0.24, 1.10)	0.65 (0.28, 1.47)	1.11 (0.55, 2.23)	—
No prior and/or concomitant remdesivir use§				
Number of participants	57	56	53	55
Recovery rate at day 29, % (95% CI)†	78.0 (66.0, 88.0)	83.8 (72.3, 92.4)	84.3 (73.1, 92.7)	83.0 (71.8, 91.6)
Recovery rate ratio vs. placebo (95% CI)¶	1.04 (0.68, 1.59)	1.16 (0.76, 1.77)	1.09 (0.72, 1.67)	—
No prior and/or concomitant glucocorticoid use§				
Number of participants	29	23	20	19
Recovery rate at day 29, % (95% CI)†	70.1 (52.7, 85.8)	88.3 (69.1, 98.0)	84.2 (65.1, 96.1)	88.1 (68.6, 98.0)
Recovery rate ratio vs. placebo (95% CI)¶	0.87 (0.42, 1.80)	1.10 (0.49, 2.50)	1.31 (0.60, 2.84)	—
>60 years old§				
Number of participants	30	29	30	31
Recovery rate at day 29, % (95% CI)†	63.6 (45.7, 81.2)	78.3 (60.7, 91.8)	78.5 (62.1, 91.3)	81.9 (65.8, 93.4)
Recovery rate ratio vs. placebo (95% CI)¶	0.60 (0.32, 1.13)	0.88 (0.49, 1.61)	0.86 (0.48, 1.54)	—
Negative for SARS-CoV-2 baseline nucleocapsid antibody§				
Number of participants	29	36	32	30
Recovery rate at day 29, % (95% CI)†	77.7 (60.8, 90.9)	81.1 (66.1, 92.3)	77.4 (61.7, 90.0)	78.5 (62.1, 91.3)
Recovery rate ratio vs. placebo (95% CI)¶	0.80 (0.40, 1.59)	0.88 (0.47, 1.66)	1.01 (0.54, 1.87)	—
All-cause mortality through day 29‖ (secondary end point)				
Number of participants	73	73	72	75
Number of deaths (%)	4 (5.5%)	5†† (6.8%)	4‡‡ (5.6%)	1 (1.3%)
Difference to placebo, % (95% CI)**	4.1 (–2.3, 12.1)	5.5 (–1.1, 13.9)	4.2 (–2.3, 12.3)	—

Data provided for the modified intent-to-treat population (i.e., all randomly assigned participants who received at least one dose of study treatment according to randomized treatment). The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects.

CI denotes confidence interval.

* Sustained recovery was defined as participants being alive and either not hospitalized (i.e., discharged from the hospital, not rehospitalized or transferred to another hospital, and not discharged to hospice care) or medically ready for hospital discharge (i.e., does not require ongoing medical care, such as home oxygen, but remains in the hospital for infection control or nonmedical reasons) through day 29.

† Calculated using the Kaplan-Meier method.

‡ Calculated using Cox regression models with treatment and randomization stratification factors as covariates; the proportional hazards assumption was met.

§ This was a retrospective analysis not prespecified in the statistical analysis plan.

¶ Calculated using Cox regression models with treatment as covariate; the proportional hazards assumption was met for all these analyses.

‖ Unknown survival status on day 29 was imputed as death for purposes of this analysis.

** Differences and confidence intervals were calculated using the Miettinen-Nurminen method.

†† One participant was imputed/analyzed as having died, but actually had unknown survival status at day 29 (withdrew consent on day 2).

‡‡ One participant was imputed/analyzed as having died, but actually had unknown survival status at day 29 (lost to follow-up on day 9).

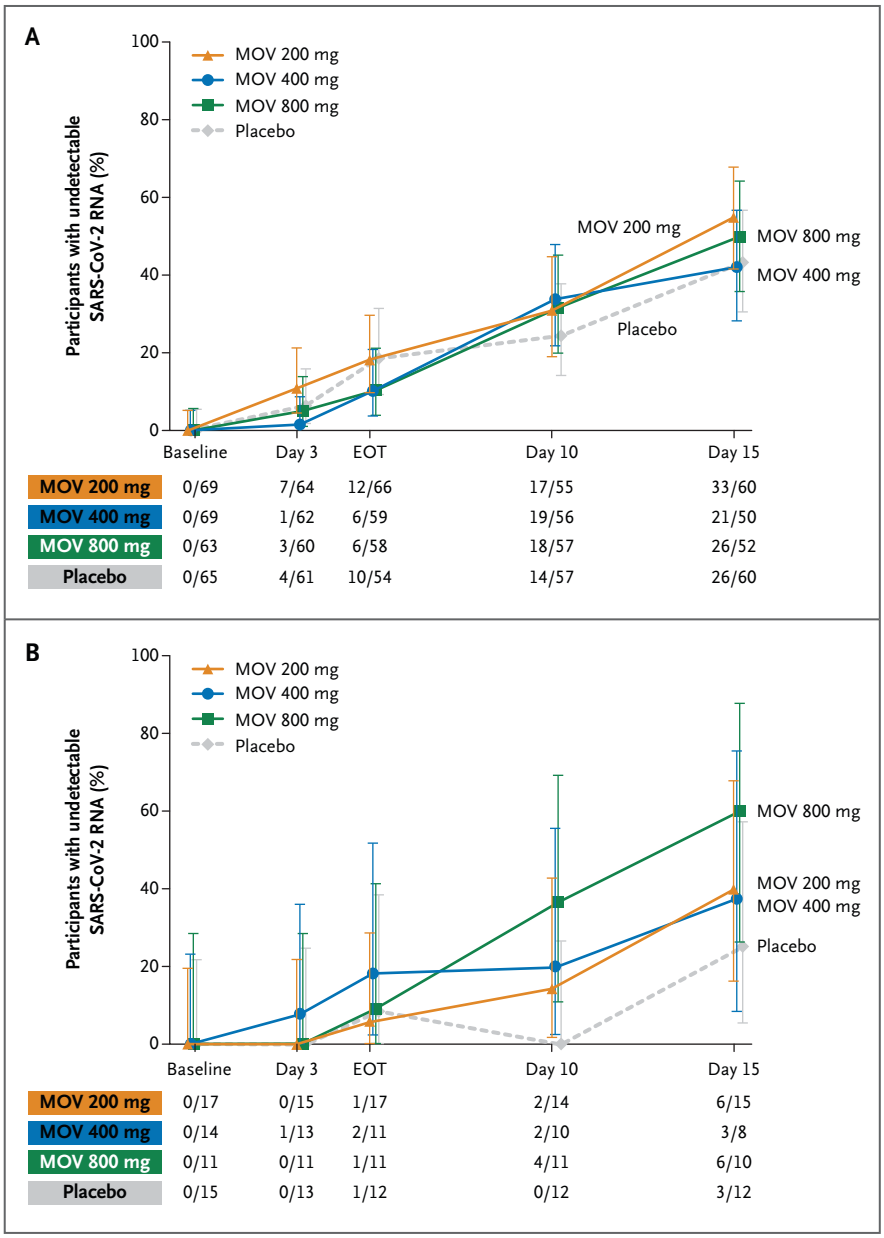

Figure 2. Undetectable SARS-CoV-2 RNA in All Participants (A) and Participants with 5 or Fewer Days Since Covid-19 Sign/Symptom Onset (B).

Assessed in modified intent-to-treat population participants (i.e., all randomly assigned participants who received at least one dose of study treatment according to randomized treatment) with baseline SARS-CoV-2 titer ≥500 copies/ml. Denominators represent number of participants eligible for this analysis and with relevant data available. MOV denotes molnupiravir.

withdrew from the trial and were conservatively imputed as having died. NHC plasma exposures were comparable to those anticipated from healthy volunteer data.[5]

It was previously found that molnupiravir and NHC increased mutation rates in the in vitro bacterial reverse mutation assay (Ames assay) and NHC in an in vitro *Hprt* assay.[19] However, in vivo studies, including data from two different, well-characterized, robust rodent mutagenicity models,[20,21] indicate that molnupiravir is not mutagenic in mammals at durations and doses (milligrams per kilogram) substantially greater than those being used in the clinic.[8] Also, molnupiravir did not induce chromosomal damage in in vitro micronucleus and in vivo rat micronucleus assays.[8]

These in vivo data provide evidence that the in vitro mutagenicity is unlikely to be biologically relevant in humans, but only clinical pharmacovigilance can provide a clear answer to this question.

In contrast to immunomodulatory drugs such as glucocorticoids,[22] tocilizumab,[23–25] baricitinib,[26,27] anakinra,[28] and otilimab,[29] nonimmunomodulatory direct antiviral treatments have not conclusively been shown to improve the survival of hospitalized patients with Covid-19 in prospective controlled clinical trials[16,30–33]; however, some of these agents retain potential therapeutic promise in certain subgroups of hospitalized patients. The most likely explanation for the difficulty of achieving clinical benefit with antivirals in the hospitalized population is the timing of treatment initiation in relation to symptom onset and disease severity. In acute respiratory infections like Covid-19, symptom onset is generally near the time of peak viral replication. In this scenario, it is reasonable to speculate that antiviral treatments should be initiated as early as possible to increase their likelihood of blunting disease progression.

In the upper respiratory tract, SARS-CoV-2 viral load peaks within 7 days, and live, replication-competent virus generally cannot be recovered after 9 to 10 days following symptom onset.[34,35] For this reason, our trial design limited eligibility to participants with 10 or fewer days of sign/symptom duration, since the host inflammatory response rather than viral load predominates Covid-19 disease processes after that time. The need for early initiation of antiviral treatment in Covid-19 is further supported by published data demonstrating clinical and virologic efficacy of convalescent plasma and monoclonal antibodies when used in the outpatient setting during very early disease (average time since symptom onset: 2 to 4 days),[36–38] while the same treatments generally lacked those benefits when used in hospitalized patients, albeit with some exceptions.[31,32]

In this phase 2 trial, a 5-day course of molnupiravir twice daily was not associated with dose-limiting side effects, but there was no signal of clinical benefit. The data from this trial, when considered alongside the positive outcomes when the same treatment was given to patients with Covid-19 but treated in an outpatient setting,[9,10] are consistent with the hypothesis that the delay in initiating treatment relative to symptom onset in this study population accounted for our inability to demonstrate a clear therapeutic benefit.

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Disclosures

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A data sharing statement provided by the authors is available at evidence.nejm.org. The data sharing policy, including restrictions, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, is available at https://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

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References

1. Yoon JJ, Toots M, Lee S, et al. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. Antimicrob Agents Chemother 2018;62:e00766-18 10.1128/AAC.00766-18.
2. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol 2021;6:11-8 10.1038/s41564-020-00835-2.
3. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med 2020;12:eabb5883 10.1126/scitranslmed.abb5883.
4. Wahl A, Gralinski LE, Johnson CE, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature 2021;591:451-7 10.1038/s41586-021-03312-w.
5. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother 2021;65:e02428-20 10.1128/AAC.02428-20.
6. Urakova N, Kuznetsova V, Crossman DK, et al. β-d-N^4-Hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome. J Virol 2018;92:e01965-17 10.1128/JVI.01965-17.
7. Abdelnabi R, Foo CS, De Jonghe S, Maes P, Weynand B, Neyts J. Molnupiravir inhibits the replication of the emerging SARS-CoV-2 variants of concern (VoCs) in a hamster infection model. J Infect Dis 2021;224:749-53 10.1093/infdis/jiab361.
8. Troth S, Butterton J, DeAnda CS, et al. Letter to the editor in response to Zhou et al. J Infect Dis 2021;224:1442-3 10.1093/infdis/jiab362.
9. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 10.1056/NEJMoa2116044.
10. Caraco Y, Crofoot G, Andres Moncada P, et al. Phase 2/3 trial of molnupiravir for treatment of Covid-19 in non-hospitalized adults. NEJM Evid DOI: 10.1056/EVIDoa2100043.
11. U.S. Food and Drug Administration. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention).
12. World Health Organization. WHO COVID-19 case definition. (https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2).
13. Tenforde MW, Billig Rose E, Lindsell CJ, et al.; CDC COVID-19 Response Team. Characteristics of adult outpatients and inpatients with COVID-19 - 11 academic medical centers, United States, March-May 2020. MMWR Morb Mortal Wkly Rep 2020;69:841-6 10.15585/mmwr.mm6926e3.
14. Docherty AB, Harrison EM, Green CA, et al.; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985 10.1136/bmj.m1985.
15. Macedo A, Gonçalves N, Febra C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol 2021;57:14-21 10.1016/j.annepidem.2021.02.012.
16. Beigel JH, Tomashek KM, Dodd LE, et al.; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813-26 10.1056/NEJMoa2007764.
17. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. medRxiv June 17, 2021 (https://www.medrxiv.org/content/10.1101/2021.06.17.21258639v1). preprint.
18. Chawla A, Cao Y, Stone J, et al. Model-based dose selection for the phase 3 evaluation of molnupiravir (MOV) in the treatment of COVID-19 in adults. ESCMID eAcademy. 2021. (https://eacademy.escmid.org/escmid/2021/eccmid-2021/332297/).
19. Zhou S, Hill CS, Sarkar S, et al. β-d-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. J Infect Dis 2021;224:415-9 10.1093/infdis/jiab247.
20. Heflich RH, Dertinger SD, Dobrovolsky VN, et al. The in vivo erythrocyte Pig-a gene mutation assay – Part 1 – detailed review paper and retrospective performance assessment. No. 315. Paris, France: Series on Testing and Assessment. Organisation for Economic Co-operation and Development, 2020. (https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2020)6&doclanguage=en).
21. Organisation for Economic Co-operation and Development. Test No. 488: Transgenic rodent somatic and germ cell gene mutation assays. OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing, 2020. (https://www.oecd-ilibrary.org/environment/test-no-488-transgenic-rodent-somatic-and-germ-cell-gene-mutation-assays_9789264203907-en). 10.1787/9789264203907-en.
22. Horby P, Lim WS, Emberson JR, et al.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693-704 10.1056/NEJMoa2021436.
23. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637-45 10.1016/S0140-6736(21)00676-0.
24. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021;384:20-30 10.1056/NEJMoa2030340.
25. Klopfenstein T, Gendrin V, Gerazime A, et al.; HNF Hospital tocilizumab multidisciplinary team. Systematic review and subgroup meta-analysis of randomized trials to determine tocilizumab's place in COVID-19 pneumonia. Infect Dis Ther 2021;10:1195-213 10.1007/s40121-021-00488-6.

26. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. (Lancet Respir Med 2021Oct:90(10):e102. 10.1016/S2213-2600(21)003331-3 (Epub ahead of print) https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v2). preprint.

27. Kalil AC, Patterson TF, Mehta AK, et al.; ACTT-2 Study Group Members. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021;384:795-807 10.1056/NEJMoa2031994.

28. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med 2021;27:1752-60 10.1038/s41591-021-01499-z.

29. Patel J, Beishuizen A, Bocca Ruiz X, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). medRxiv April 17, 2021 (https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1). preprint.

30. Pan H, Peto R, Henao-Restrepo AM, et al.; WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med 2021;384:497-511 10.1056/NEJMoa2023184.

31. ACTIV-3/TICO LY-CoV555 Study Group; Lundgren JD, Grund B, Barkauskas CE, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. N Engl J Med 2021;384:905-14. 10.1056/NEJMoa2033130.

32. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049-59 10.1016/S0140-6736(21)00897-7.

33. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020;396:1345-52 10.1016/S0140-6736(20)32013-4.

34. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe 2021;2:e13-22 10.1016/S2666-5247(20)30172-5.

35. Jones TC, Biele G, Mühlemann B, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. Science 2021;373: eabi5273 10.1126/science.abi5273.

36. Libster R, Pérez Marc G, Wappner D, et al.; Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. N Engl J Med 2021;384:610-8 10.1056/NEJMoa2033700.

37. Weinreich DM, Sivapalasingam S, Norton T, et al.; Trial Investigators. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238-51 10.1056/NEJMoa2035002.

38. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325:632-44 10.1001/jama.2021.0202.