# 2 SYNOPSIS

**SPONSOR:** Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

**COMPOUND NAME:** Molnupiravir (MOV; MK-4482)

**PROTOCOL TITLE:** A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19

**STUDY IDENTIFIERS:**

| | | | |
|---|---|---|---|
| IND: 147734 | EudraCT: 2020-003367-26 | WHO: N/A | NCT: 04575584 |

**STUDY PHASE:** 2/3

**INDICATION:** Treatment of COVID-19

**STUDY CENTERS:** This study was conducted at 86 centers in 15 countries.

**STUDY STATUS:** This study is ongoing; this report is based on interim analysis 2 (IA2) data for Part 1 (Phase 2).

| First Patient, First Visit | Last Patient, Last Visit | Data Cut-off or Database Lock Date |
|---|---|---|
| 19-OCT-2020 | 12-FEB-2021 | 11-MAR-2021 |

NOTE: Patient = Participant

**METHODOLOGY:** This is a Phase 2/3, randomized, placebo-controlled, double-blind, multisite study to evaluate the efficacy, safety, and pharmacokinetics (PK) of molnupiravir (MOV or MK-4482) administered to hospitalized participants ≥18 years of age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with signs/symptoms attributable to coronavirus disease 2019 (COVID-19).

The study was to be conducted in 2 parts: Part 1 (Phase 2 - Dose Ranging) and Part 2 (Phase 3 - Evaluation of Selected Dose). In Part 1, 304 participants with an initial onset of signs/symptoms attributable to COVID-19 ≤10 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization were enrolled. Participants were randomized in a 1:1:1:1 ratio into 1 of 4 intervention groups: MOV 200 mg, MOV 400 mg, MOV 800 mg, or placebo. Intervention randomization was stratified according to time from symptom onset prior to the day of randomization (≤5 days, >5 days), age (≤60 years, >60 years), and remdesivir use for treatment of the index diagnosis of COVID-19 prior to or at the time of randomization (yes, no). Sponsor-designated standard of care treatment of COVID-19, which included remdesivir, systemic corticosteroids, and convalescent plasma, was permitted.

Participants received assigned study intervention by oral administration for 5 days once every 12 hours (Q12H), and were followed for 28 days after randomization (through Day 29) for the primary endpoint. Events of clinical interest (ECI) included transaminase elevations suggestive of drug-induced liver injury (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN], total bilirubin ≥2x ULN, and alkaline phosphatase < 2x ULN), platelet count of <50,000/µL, and amylase or lipase values >3x ULN.

This report is based on IA2, which was conducted after all Part 1 participants completed Day 29. Data from IA2 indicated that MOV is unlikely to demonstrate a clinical benefit in a clinical study enrolling hospitalized participants, who generally have a long duration of symptoms (>5 days) prior to study entry; therefore, this study will not proceed to Part 2 (Phase 3). Part 1 participants will continue to be followed until Month 7. Data for participants in Part 1 through the 7-month follow-up period will be provided in a separate report.

The study interventions administered in Part 1 are presented in the following table.

**Intervention Groups and Duration**

| Intervention Group Name | Dose Frequency | Route of Administration | Treatment Period |
|---|---|---|---|
| MOV 200 mg | Q12H | Oral | 5 days (10 doses total) |
| MOV 400 mg | Q12H | Oral | 5 days (10 doses total) |
| MOV 800 mg | Q12H | Oral | 5 days (10 doses total) |
| Placebo | Q12H | Oral | 5 days (10 doses total) |
| MOV=molnupiravir; Q12H=once every 12 hours | | | |

## ELIGIBILITY CRITERIA:

Male or female participants ≥ 18 years of age with laboratory-confirmed SARS-CoV-2 infection with sample collection ≤10 days prior to randomization who met the following key inclusion criteria were eligible to participate in the study:

- Had initial onset of signs/symptoms attributable to COVID-19 for ≤10 days prior to the day of randomization and ≥1 sign/symptom attributable to COVID-19 present at randomization.
- Required medical care in the hospital for ongoing clinical manifestations of COVID-19 (not only for public health or quarantine purposes).
- Had mild, moderate, or severe COVID-19 as defined in Appendix 9 of the protocol.

**OBJECTIVES AND ENDPOINTS:**

| Primary Objectives | Primary Endpoints |
|---|---|
| - To evaluate the efficacy of MOV compared to placebo as assessed by the rate of sustained recovery from randomization through Day 29. | - Time-to-sustained recovery |
| - To evaluate the safety and tolerability of MOV compared to placebo. | - Adverse events<br>- Adverse events leading to discontinuation of study intervention |
| Secondary Objectives | Secondary Endpoints |
| - To evaluate the efficacy of MOV compared to placebo as assessed by the percentage of participants who die through Day 29. | - All-cause mortality |
| - To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on selected ordinal outcome scales at Day 3, EOT, Day 10, Day 15, and Day 29. | - Pulmonary score<br>- Pulmonary+ score |
| - To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response in the clinical risk of mortality category from the National Early Warning Score at EOT. | - National Early Warning Score |
| - To evaluate the efficacy of MOV compared to placebo as assessed by the odds of a more favorable response on the WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15, and Day 29. | - WHO 11-point scale score |

**NUMBER OF PARTICIPANTS (planned and analyzed):** The planned enrollment total for Part 1 was approximately 300 participants. A total of 304 participants were randomized as follows: 75 participants (MOV 200 mg), 75 participants (MOV 400 mg), 76 participants (MOV 800 mg), 78 participants (placebo).

**STATISTICAL ANALYSIS METHODS:** The primary population for efficacy analyses was the modified intent-to-treat (MITT) population, which consisted of all randomized participants who received at least 1 dose of study intervention. Participants were included in the intervention group to which they were randomized. The primary efficacy analysis compared MOV 200 mg, MOV 400 mg, and MOV 800 mg, and placebo with respect to time-to-sustained recovery by Day 29 using a stratified log-rank test. The sustained recovery

rate ratio was estimated using the stratified Cox proportional hazards regression model. No formal hypothesis testing was performed in Part 1 of the study.

The change from baseline in SARS-CoV-2 RNA titer, calculated as $\log_{10}$ (post) minus $\log_{10}$ (baseline), as measured by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) of samples from nasopharyngeal (NP) and oropharyngeal (OP) swabs was summarized separately by intervention group and time point. Treatment differences in change in SARS-CoV-2 RNA titer from baseline over time were estimated using longitudinal models.

Safety analyses were based on the All Participants as Treated (APaT) population, which included 293 randomized participants who received at least 1 dose of study intervention. Participants were included in the intervention group corresponding to the study treatment they actually received.

**RESULTS:**

**Disposition, Demographics and Baseline Characteristics**

**Number of participants randomized /treated/discontinued:**

- MOV 200 mg: 75 randomized/ 73 treated/ 3 discontinued study intervention/ 62 followed through Day 29.
- MOV 400 mg: 75 randomized/ 73 treated/ 7 discontinued study intervention/ 60 followed through Day 29.
- MOV 800 mg: 76 randomized/ 72 treated/ 3 discontinued study intervention/ 66 followed through Day 29.
- Placebo group: 78 randomized/ 75 treated/ 3 discontinued study intervention/ 70 followed through Day 29.

**Overall Mean Age (range):** 57.0 years (19 to 94 years)

**Sex:** 172 (56.6%) male, 132 (43.4%) female

**Ethnicity:** 184 (60.5%) not Hispanic or Latino, 114 (37.5%) Hispanic or Latino, 4 (1.3%) not reported, 2 (0.7%) unknown.

**Race:** 6 (2.0%) American Indian or Alaska Native, 23 (7.6%) Asian, 18 (5.9%) black or African-American, 27 (8.9%) other/multiple, 1 (0.3%) Native Hawaiian or Other Pacific Islander, 227 (74.7%) white, 2 (0.7%) unknown

**Efficacy:**

- The observed rate of sustained recovery through Day 29 was high overall and similar in the MOV groups compared with placebo.
- There was a higher number of deaths in participants in each MOV group compared with placebo.
- Improvement in outcomes over time, as assessed by the Pulmonary ordinal scale, Pulmonary+ ordinal scale, National Early Warning score (NEWS), and World Health

Organization (WHO) 11-point scale, were similar in the MOV groups compared with placebo.

- Similar decreases from baseline in mean SARS-CoV-2 RNA titers in NP and OP samples, as assessed by quantitative PCR, were observed in the MOV groups compared with placebo at all timepoints.
- The proportion of participants with undetectable SARS-CoV-2 RNA in NP and OP samples over time, as assessed by a qualitative PCR assay, was generally similar across all intervention groups.
- Consistent with the mechanism of action of MOV (viral error catastrophe), an increased SARS-CoV-2 mutation rate was observed by Day 3 or Day 5 in NP swabs in participants receiving any dose of MOV compared with placebo.

**Safety:**

- The overall safety profiles observed were generally comparable for MOV at all doses studied and placebo. No trends in incidence of adverse events (AEs) by MOV dose were observed.
- Study intervention-related serious adverse events (SAEs) and discontinuation of study intervention due to an AE were infrequent and the proportions of participants experiencing these AEs were comparable across intervention groups.
- The most frequently reported AEs (>5%) in any of the MOV intervention groups were COVID-19, AST/ALT elevations, constipation, bacterial pneumonia, hyperglycemia, and respiratory failure.
- The most frequently reported AEs (>5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased, and respiratory failure.
- A total of 16 participants had AEs resulting in death by Day 15. A higher number of AEs resulting in death were reported in the MOV groups compared with the placebo group. None of the deaths were considered to be related to study intervention per investigator assessment.
- No evidence of hematologic, pancreatic, or hepatic toxicity was observed for MOV.

# Adverse Event Summary
# During Treatment and 14-Day Follow-Up Period
# All Participants as Treated Population
# MK-4482-001 IA2

| | MK-4482 200 mg | | MK-4482 400 mg | | MK-4482 800 mg | | MK-4482 Combined | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 73 | | 73 | | 72 | | 218 | | 75 | | 293 | |
| with one or more adverse events | 40 | (54.8) | 36 | (49.3) | 45 | (62.5) | 121 | (55.5) | 46 | (61.3) | 167 | (57.0) |
| with no adverse event | 33 | (45.2) | 37 | (50.7) | 27 | (37.5) | 97 | (44.5) | 29 | (38.7) | 126 | (43.0) |
| with drug-related[a] adverse events | 8 | (11.0) | 6 | (8.2) | 10 | (13.9) | 24 | (11.0) | 16 | (21.3) | 40 | (13.7) |
| with serious adverse events | 11 | (15.1) | 9 | (12.3) | 13 | (18.1) | 33 | (15.1) | 12 | (16.0) | 45 | (15.4) |
| with serious drug-related adverse events | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.3) |
| who died | 6 | (8.2) | 4 | (5.5) | 4 | (5.6) | 14 | (6.4) | 2 | (2.7) | 16 | (5.5) |
| discontinued drug due to an adverse event | 0 | (0.0) | 1 | (1.4) | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.3) |
| discontinued drug due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to a serious adverse event | 0 | (0.0) | 1 | (1.4) | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.3) |
| discontinued drug due to a serious drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[a] Determined by the investigator to be related to the drug.

Source: [P001V01MK4482: adam-adsl; adae]

**CONCLUSIONS:**

Results from IA2 in hospitalized participants randomized ≤10 days of COVID-19 symptom onset indicate:

- No clear effect of MOV treatment on sustained recovery was observed.
- All MOV doses studied were generally well tolerated.

**PUBLICATION(S):** As of the date of this report, there are no publications based on this study.

**REPORT DATE: 19-JUL-2021**