2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, 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: NCT04575584

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 complete; this report is based on the final analysis.

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
19-OCT-2020	11-AUG-2021	10-NOV-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. SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29.

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 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.

Data from interim analysis 2 (IA2), which was conducted after all Part 1 participants completed Day 29, showed that MOV was unlikely to have a clinical benefit in hospitalized study participants who generally have a long duration of symptoms (>5 days) prior to study entry. Therefore, this study did not proceed to Part 2 (Phase 3). Part 1 participants were followed until the Late Follow-up visit (LFU) (Month 7).

The P001V01MK4482 clinical study report (CSR) reported key results from IA2. This CSR reports the following:

- Data collected through the LFU visit
  - Survival status and hospitalizations recorded from Day 30 through the LFU visit
  - Supplemental oxygen use at the LFU visit
- Planned data summaries that were not previously presented in the P001V01MK4482 CSR due to its interim nature
  - Protocol deviations
  - Baseline clade distribution
  - Medical history
  - Prior and concomitant medications
  - Study intervention compliance
  - Nucleotide transition and transversion analysis
  - Treatment-emergent amino acid variant analysis
  - Viral infectivity
  - Inflammatory biomarkers

- Updated analyses

  - Updated analysis of the incidence of all-cause mortality (secondary endpoint) to include Day 29 survival status obtained after the data cutoff for the P001V01MK4482 CSR.

  - Updated analysis of SARS-CoV-2 RNA mutation rate to include additional postbaseline SARS-CoV-2 viral sequence data that were not available as of the data cutoff for the P001V01MK4482 CSR.

This study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its standard operating procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

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

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:

The following objectives were evaluated in hospitalized adults with COVID-19. No formal hypothesis testing was performed in Part 1 of the study.

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 ▪ 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 ▪ 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

In addition to the endpoints listed above, survival and hospitalization status reported from Day 30 through the LFU visit (Month 7) and supplemental oxygen use at the LFU visit were summarized.

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 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.

Data collected through the LFU visit (survival and hospitalization status reported from Day 30 through the LFU visit [Month 7] and supplemental oxygen use at the LFU visit) were also summarized.

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 (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 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:

Disposition through the Day 29 visit and demographics and baseline characteristics were presented in the P001V01MK4482 CSR.

Number of Participants Randomized/Followed Through LFU Visit (Month 7):

- MOV 200 mg: 75 randomized/ 61 followed through the LFU Visit (Month 7).
- MOV 400 mg: 75 randomized/ 60 followed through the LFU Visit (Month 7).
- MOV 800 mg: 76 randomized/ 63 followed through the LFU Visit (Month 7).

- Placebo group: 78 randomized/ 70 followed through the LFU Visit (Month 7).

Efficacy:

Summary of Efficacy Data Through Day 29 Presented in the P001V01MK4482 CSR

- The observed rate of sustained recovery through Day 29 was high overall and similar in each of the MOV groups compared with placebo.

- There was a higher number of deaths in each of the MOV groups compared with placebo.

- Improvements in outcomes over time, as assessed by the Pulmonary ordinal scale, Pulmonary+ ordinal scale, National Early Warning score, and World Health Organization 11-point scale, were similar in each of 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 each of 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 in each of the MOV groups compared with placebo.

Summary of Efficacy Data Through Day 29 Presented in this CSR
(based on data updates or data summaries that were not included in the P001V01MK4482 CSR):

- The number of deaths was low overall; a higher number of participants died in each of the MOV groups compared with placebo.

- 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 in each of the MOV groups compared with placebo.

- No treatment-emergent amino acid substitutions were detected in 2 or more participants in any of the replicase complex genes (nsp7-14) in paired baseline and postbaseline NP and OP samples of participants in the combined MOV group.

- Treatment with MOV at each dose reduced the percentage of participants with infectious virus in NP samples compared with placebo by Day 3.

- The mean change from Baseline to Day 5 for inflammatory biomarkers (interleukin-6, high-sensitivity c-reactive protein, erythrocyte sedimentation rate, D-dimer, and procalcitonin) was generally comparable in each of the MOV groups compared with placebo.

Summary of Data Through the LFU Visit

- Overall, 6 participants were re-hospitalized from Day 30 though the LFU visit (3 in the MOV combined group and 3 in the placebo group).

- Overall, 6 participants died from Day 30 though the LFU visit (5 in the MOV combined group and 1 in the placebo group).

- Supplemental oxygen use was reported for 2 participants (1 in the MOV 800 mg group and 1 in placebo) at the LFU visit.

Safety:

Summary of Safety Presented in the P001V01MK4482 CSR

- The overall safety profiles observed were generally comparable for MOV at each dose 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 each 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.

- Overall, 16 participants had AEs resulting in death. A higher number of AEs resulting in death were reported in each of 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.

Summary of Safety Through the LFU Visit

- From 14 days after the last dose of study intervention through the LFU visit (Month 7), no intervention-related SAEs were reported.

CONCLUSIONS:

In hospitalized participants randomized ≤10 days of COVID-19 symptom onset:

- No clear effect of MOV treatment on sustained recovery was observed.

- All MOV doses studied were generally well tolerated.

PUBLICATION(S):

Arribas J, Bhagani S, Lobo S, Khaertynova I, Mateu L, Fishchuk R, et al. Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19. N Engl J Med Evid. 2021 Dec 16.

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