2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: Molnupiravir (MK-4482)

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-4482 for the Prevention of COVID-19 (Laboratory-confirmed SARS-CoV-2 Infection With Symptoms) in Adults Residing With a Person With COVID-19.

STUDY IDENTIFIERS:

IND: 155588	EudraCT: 2021-000904-39	WHO:Not applicable	NCT: 04939428
JRCT: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 3

INDICATION: Viral infection, COVID-19 prophylaxis

STUDY CENTERS: This study was conducted at 226 centers in 23 countries.

STUDY STATUS:

This study is complete; this report is based on the final analysis.

First Participant, First Visit	Last Participant, Last Visit	Database Lock Date
11-AUG-2021	16-NOV-2022	08-FEB-2023

METHODOLOGY:

This was a Phase 3, randomized, placebo-controlled, double-blind, multicenter interventional study to evaluate the efficacy and safety of MOV to prevent COVID-19 in participants ≥18 years of age residing with an individual (no age requirement) with COVID-19 (defined as the index case). Eligible participants who did not have confirmed or suspected COVID-19 at the time of screening and randomization must have been enrolled within 5 days of both (1) sample collection for the index case's first detectable (ie, positive) SARS-CoV-2 test result, and (2) the onset of the index case's COVID-19 symptoms. Index cases were enrolled but not randomized to study intervention and had no study specific assessments or procedures other than an optional NP (or OP) swab collected at screening for viral characterization.

Participants were randomized in a 1:1 ratio to receive blinded MOV (800 mg) or matching placebo by oral administration Q12H (±2 hours) for 5 days. Randomization was stratified by 1) age category (≤60 vs >60 years) and 2) household size (≤3 vs >3 household residents; all residents, including the index case, were counted regardless of whether they were participating in the study). Active surveillance was conducted for onset of symptoms attributable to COVID-19. Participants were followed for 29 days for the evaluation of efficacy, safety, virology, serology, health care utilization, and health outcomes.

The study interventions administered are presented in the following table.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/	Use
Group 1	MOV (MK-4482)	200 mg	800 mg	Oral	Q12H (+/-2 hours) for 5 days (10 doses total)	Test Product
Group 2	Matching Placebo	0 mg	N/A	Oral	Q12H (+/-2 hours) for 5 days (10 doses total)	Placebo

MOV=molnupiravir; N/A=not applicable; Q12H=once every 12 hours

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.

ELIGIBILITY CRITERIA:

Male and female participants ≥18 years of age who did not have confirmed or suspected COVID-19 at the time of screening and randomization, were not vaccinated against SARS-CoV-2, and were household contacts of an index case. An index case was a person with documented COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) and must have had:

- A first detectable SARS-CoV-2 test result from a sample collected ≤5 days prior to randomization of the participant(s), AND

- At least 1 symptom attributable to COVID-19 (eg, fever, difficulty breathing) with symptom onset no earlier than 5 days prior to randomization of the participant(s).

OBJECTIVES AND ENDPOINTS:

Objectives were evaluated in participants ≥18 years of age who did not have confirmed or suspected COVID-19 at the time of screening and randomization and were residing with an individual (of any age) with COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms), defined as the index case.

Primary Objective	**Primary Endpoint**
- To evaluate the efficacy of molnupiravir (MOV) compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline nasopharyngeal (NP) swabs. - *Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline NP swabs.*	- COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
- To evaluate the safety and tolerability of MOV compared with placebo.	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
- To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants regardless of SARS-CoV-2 results in baseline NP swabs. - *Hypothesis: MOV is superior to placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in all participants regardless of SARS-CoV-2 results in baseline NP swabs*.	- COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
- To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 29 in participants with undetectable SARS-CoV-2 in baseline NP swabs.	- COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)
- To evaluate prevention of viral transmission through Day 14 for MOV compared with placebo in participants with undetectable SARS-CoV-2 in baseline NP swabs.	- SARS-CoV-2 RNA

- To evaluate the efficacy of MOV compared with placebo for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants with detectable SARS-CoV-2 in baseline NP swabs.	- COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms)

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 1376 participants. As of database lock, 1539 participants were randomized (768 participants MOV 800 mg and 771 participants placebo). Because baseline SARS-CoV-2 viral status was not known at the time of randomization, additional participants were enrolled to ensure that the specified target of at least 1100 participants with undetectable SARS-CoV-2 in baseline swabs was met for primary and supportive analyses of the primary endpoint. Ultimately, 630 participants receiving MOV and 634 receiving placebo were available for the primary analysis.

STATISTICAL AND ANALYSIS METHODS:

The primary population for efficacy analyses was the mITT population which consisted of all randomized participants who received ≥1 dose of study intervention; participants were analyzed by the intervention group to which they were randomized. The primary efficacy analysis was conducted in the mITT-VN population. The superiority of MOV compared with placebo was evaluated at the α=0.025 (1-sided) level with respect to the percentage of participants with undetectable SARS-CoV-2 in baseline NP swabs developing COVID-19 by Day 14 using the stratified Miettinen and Nurminen method with Cochran-Mantel-Haenszel weights.

Safety analyses were based on the APaT, which included all randomized participants in the study who received at least 1 dose of study treatment; participants were included in the intervention group corresponding to the study treatment they actually received. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

RESULTS:

Participant Disposition:

- MOV group: 768 randomized, 763 treated, 750 completed treatment, 13 discontinued treatment, 750 completed the study, 18 discontinued from the study.

- Placebo group: 771 randomized, 765 treated, 755 completed treatment, 10 discontinued treatment, 751 completed the study, 20 discontinued from the study.

Demographics and Baseline Characteristics:

Data reflect all randomized participants:

- **Overall Median Age (Range):** 37.0 years (18 to 96 years)
- **Sex:** 708 (46.0%) male, 831 (54.0%) female
- **Ethnicity:** 875 (56.9%) not Hispanic or Latino, 663 (43.1%) Hispanic or Latino, 1 (0.1%) not reported/unknown/missing
- **Race:** 899 (58.4%) white, 248 (16.1%) multiple, 175 (11.4%) American Indian or Alaska Native, 122 (7.9%) black or African American, 88 (5.7%) Asian, 5 (0.3%) Native Hawaiian or other Pacific Islander, 2 (0.1%) unknown.

Additional Baseline Characteristics:

- 180 (11.7%) participants were >60 years of age
- 999 (64.9%) participants were from household size of >3 residents
- 232 (15.1%) participants had detectable baseline SARS-CoV-2 RNA (NP sample)
- 1286 (83.6%) participants had positive anti-nucleocapsid and/or neutralizing (anti-spike-protein) SARS-CoV-2 antibody at baseline

Efficacy:

Primary Efficacy Endpoint

- In the mITT-VN population, the percentage of participants who developed COVID-19 through Day 14 in the MOV group was not statistically significantly lower compared with the placebo group (MOV 41/630 [6.5%] vs placebo 54/634 [8.5%]; adjusted difference in rates [95% CI]: -2.0 [-5.0, 0.9]; p-value=0.0848). The protocol-defined success criterion for demonstration of superiority to placebo (1-sided p-value boundary) was p<0.0249.

Secondary Efficacy Endpoints

- The percentage of participants in the mITT population (regardless of SARS-CoV-2 baseline results) who developed COVID-19 through Day 14 was lower in the MOV group compared with the placebo group (MOV: 10.2%, placebo: 13.5%) with adjusted difference in rates (95% CI):-3.2 (-6.3, -0.1), unadjusted p=0.0205. As the success criterion for the primary hypothesis/endpoint was not met, the analysis of the secondary endpoint is unadjusted for multiplicity and is provided for descriptive purposes only.

- The percentage of participants in the mITT-VN population (undetectable SARS-CoV-2 in baseline NP swabs) who developed COVID-19 through Day 29 was consistent with the results of the primary endpoint (MOV: 8.1%, placebo: 10.3%; adjusted difference in rates [95% CI]: -2.2 [-5.4, 1.0]).

- In the mITT-VN population, a lower observed percentage of participants had onset of detectable SARS-CoV-2 infection (regardless of symptoms) through Day 14 in the MOV group (11.4%) compared with the placebo group (14.4%), although the 95% CI of the adjusted difference in rates included zero (adjusted difference in rates [95% CI]: -3.0 [- 6.9, 0.8]).

- In the mITT-VP population (detectable SARS-CoV-2 in baseline NP swabs), a lower observed percentage of participants developed COVID-19 through Day 14 in the MOV group (30.7%) compared with the placebo group (41.2%), although the 95% CI of the adjusted difference in rates included zero (adjusted difference in rates [95% CI]: -10.5 [-22.7, 2.0]).

Safety:

Overall, the safety profile of MOV 800 mg Q12H for 5 days was comparable with placebo.

Overall AEs

- The percentage of participants with 1 or more reported AEs was comparable between intervention groups.

- The most frequently reported AEs (≥1% in either group, MOV vs placebo) were nasopharyngitis (2.0% vs 1.2%), and blood creatine phosphokinase increased (0.8% vs 1.4%). No trends in AEs by intervention group were observed.

- The percentage of participants with reported AEs considered related to study intervention by the investigator was low and comparable between intervention groups.

SAEs and Other Clinically Meaningful AEs

- One (0.1%) participant in the placebo group died due to an AE (acute myocardial infarction). The death was not considered to be related to study intervention by the investigator.

- The percentage of participants with reported SAEs was low and comparable between intervention groups. No SAEs were considered to be related to study intervention by the investigator.

- The percentage of participants with AEs leading to study intervention discontinuation was low and comparable between intervention groups.

- The percentage of participants with laboratory values that met predefined limits of change was comparable between intervention groups.

Analysis of Adverse Event Summary
During Treatment and 14-Day Follow-Up Period
All Participants as Treated Population

	MK-4482 800 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	763		765		
with one or more adverse events	94	(12.3)	105	(13.7)	-1.4 (-4.8, 2.0)
with no adverse event	669	(87.7)	660	(86.3)	1.4 (-2.0, 4.8)
with drug-related[b] adverse events	13	(1.7)	14	(1.8)	-0.1 (-1.5, 1.3)
with serious adverse events	3	(0.4)	2	(0.3)	0.1 (-0.6, 0.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.5, 0.5)
who died	0	(0.0)	1	(0.1)	-0.1 (-0.7, 0.4)
discontinued drug due to an adverse event	3	(0.4)	1	(0.1)	0.3 (-0.4, 1.0)
discontinued drug due to a drug-related adverse event	3	(0.4)	0	(0.0)	0.4 (-0.1, 1.1)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-0.5, 0.5)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.5, 0.5)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Source: [P013MK4482: adam-adsl; adae]

CONCLUSIONS:

Efficacy

Based on the results from this study, the following key efficacy results were observed:

- MOV did not meet the protocol-defined success criterion for demonstration of superiority to placebo for the primary efficacy endpoint of prevention of development of COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline NP swabs.

Safety

Based on the results from this study, the following safety conclusion can be made:

- MOV 800 mg Q12H for 5 days is generally well tolerated.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
AE	adverse event
APaT	all participants as treated
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
LPLV	last participant, last visit
mITT	modified intent-to-treat
mITT-VN	subset of modified intent-to-treat population with undetectable SARS-CoV-2 in baseline nasal swabs
mITT-VP	subset of modified intent-to-treat population with detectable SARS-CoV-2 in baseline nasal swabs
MOV	molnupiravir (MK-4482)
NP	Nasopharyngeal
Q12H	once every 12 hours
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure

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

REPORT DATE: 22-JUN-2023

REVISED REPORT DATE: Not applicable.