Clinical trial results:
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

Summary

EudraCT number	2021-000904-39
Trial protocol	ES FR HU BG RO
Global end of trial date	16 November 2022

Results information

Result version number	v1
This version publication date	22 November 2023
First version publication date	22 November 2023

Trial information

Trial identification

Sponsor protocol code	4482-013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04939428
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT (Japan Registry of Clinical Trials): jRCT2031210281, EudraCT: 2021-000904-39, PHRR: PHRR211007-003980

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2022
Global end of trial reached?	Yes
Global end of trial date	16 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to assess if the study medication (molnupiravir, MK-4482) would prevent symptomatic coronavirus disease 2019 (COVID-19) in adults who lived with someone with confirmed COVID-19 infection. This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study; half of the study participants received molnupiravir twice daily by mouth and the other half received a placebo. The primary objectives of the study were to determine if molnupiravir prevented symptomatic COVID-19 disease and to evaluate its safety and tolerability. All participants who developed COVID-19 during the study were still eligible for any COVID-19 treatment recommended by their doctor.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Bulgaria: 73
Country: Number of subjects enrolled	Colombia: 214
Country: Number of subjects enrolled	Egypt: 74
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Guatemala: 22
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Japan: 22
Country: Number of subjects enrolled	Kenya: 5
Country: Number of subjects enrolled	Mexico: 161
Country: Number of subjects enrolled	Philippines: 21
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Russian Federation: 175
Country: Number of subjects enrolled	South Africa: 119
Country: Number of subjects enrolled	Thailand: 9

Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 164
Country: Number of subjects enrolled	United States: 409
Worldwide total number of subjects	1539
EEA total number of subjects	121

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1416
From 65 to 84 years	116
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Only eligible participants without confirmed or suspected COVID-19 were enrolled within a 5-day period of the index case's first positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result and COVID-19 symptoms onset.

Pre-assignment

Screening details:

Index cases did not receive study intervention, and only had an optional swab collected at screening for viral testing and SARS-COV2 genetic lineage identification. Baseline characteristics were collected, but no outcome data was gathered.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Molnupiravir

Arm description:

Participants were treated with molnupiravir 800 mg every 12 hours (Q12H) on Days 1 to 5.

Arm type	Experimental
Investigational medicinal product name	Molnupiravir
Investigational medicinal product code	
Other name	MK-4482-013
Pharmaceutical forms	Capsule, Capsule
Routes of administration	Oral use, Oral use

Dosage and administration details:

Participants were treated with molnupiravir 800 mg every 12 hours (Q12H) on Days 1 to 5

Arm title	Placebo

Arm description:

Participants were given placebo Q12H on Days 1 to 5.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were given placebo Q12H on Days 1 to 5.

Number of subjects in period 1	Molnupiravir	Placebo
Started	768	771
Treated	763	765
Completed	750	751
Not completed	18	20
Physician decision	1	-
Consent withdrawn by subject	10	11
Randomized By Mistake Without Study Treatment	1	-
Death	-	1
Lost to follow-up	-	5
Unkown	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Molnupiravir
Reporting group description:	
Participants were treated with molnupiravir 800 mg every 12 hours (Q12H) on Days 1 to 5.	
Reporting group title	Placebo
Reporting group description:	
Participants were given placebo Q12H on Days 1 to 5.	

Reporting group values	Molnupiravir	Placebo	Total
Number of subjects	768	771	1539
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	707	709	1416
From 65-84 years	57	59	116
85 years and over	4	3	7
Age Continuous Units: years			
median	37.0	37.0	
standard deviation	± 15.6	± 15.5	-
Gender Categorical Units: Subjects			
Female	366	342	708
Male	402	429	831
Race Units: Subjects			
American Indian Or Alaska Native	85	90	175
Asian	48	40	88
Black Or African American	62	60	122
Native Hawaiian Or Other Pacific Islander	1	4	5
White	453	446	899
Multiple	119	129	248
Missing	0	2	2
Ethnicity Units: Subjects			
Hispanic Or Latino	323	340	663
Not Hispanic Or Latino	445	430	875
Not Reported	0	1	1
Stratification Factor at Randomization Collected via IRT: Household Size			

Units: Subjects			
<=3	269	271	540
>=3	499	500	999
Stratification Factor at Randomization Collected via IRT: Age Group Units: Subjects			
<=60	680	680	1360
>=60	88	91	179

End points

End points reporting groups

Reporting group title	Molnupiravir
Reporting group description:	
Participants were treated with molnupiravir 800 mg every 12 hours (Q12H) on Days 1 to 5.	
Reporting group title	Placebo
Reporting group description:	
Participants were given placebo Q12H on Days 1 to 5.	

Primary: Percentage of Participants who Had Undetectable SARS-CoV-2 in Baseline Nasopharyngeal (NP) Swabs and Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection With Symptoms) Through Day 14

End point title	Percentage of Participants who Had Undetectable SARS-CoV-2 in Baseline Nasopharyngeal (NP) Swabs and Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection With Symptoms) Through Day 14
End point description:	
Percentage of participants who had undetectable SARS-CoV-2 in baseline NP swabs and developed COVID-19 (laboratory-confirmed SARS-CoV-2) infection with symptoms) through Day 14. Efficacy analysis was conducted on the mITT (modified intent to treat) population consisting of all randomized participants who received at least 1 dose of study intervention.	
End point type	Primary
End point timeframe:	
Day 14	

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	630	634		
Units: Percentage of Participants				
number (not applicable)	41	54		

Statistical analyses

Statistical analysis title	COVID-19 at Day 14 With no SARS-CoV-2 at Baseline
Statistical analysis description:	
Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by age and household size.	
Comparison groups	Molnupiravir v Placebo

Number of subjects included in analysis	1264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0848
Method	Miettinen & Nurminen method
Parameter estimate	Confidence Interval
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	0.9

Primary: Percentage of Participants Discontinuing From Study Therapy due to AE

End point title	Percentage of Participants Discontinuing From Study Therapy due to AE

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Safety Analyses was conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Up to 5 days

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	763	765		
Units: Participants	3	1		

Statistical analyses

Statistical analysis title	Percentage of Participants Discontinued due to AE

Statistical analysis description:

95% CIs (Tier 2 endpoints) was provided for between treatment differences in the percentage of participants with events; these analyses was performed using the Miettinen and Nurminen method.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	1528
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Miettinen & Nurminen method.
Parameter estimate	Confidence Interval
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1

Notes:

[1] - Estimated differences and confidence intervals are provided

Primary: Percentage of Participants With ≥1 Adverse Event

End point title	Percentage of Participants With ≥1 Adverse Event

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Safety Analyses was conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

29 days

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	763	765		
Units: Participants	94	105		

Statistical analyses

Statistical analysis title	Percentage of Participants with Adverse Events

Statistical analysis description:

95% CIs (Tier 2 endpoints) was provided for between treatment differences in the percentage of participants with events; these analyses was performed using the Miettinen and Nurminen method.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	1528
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Miettinen & Nurminen method
Parameter estimate	Confidence Interval
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2

Notes:

[2] - Estimated differences and confidence intervals are provided.

Secondary: Percentage of Participants (Regardless of SARS-CoV-2 in Baseline NP

Swabs) who Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection with Symptoms) Through Day 14

End point title	Percentage of Participants (Regardless of SARS-CoV-2 in Baseline NP Swabs) who Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection with Symptoms) Through Day 14

End point description:

Participants who experienced targeted symptoms of COVID-19 (e.g., cough, sore throat) and had NP swabs tested for SARS-CoV-2 using reverse-transcription polymerase chain reaction (RT-PCR).Efficacy analysis was conducted on the mITT (modified intent to treat) population consisting of all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	763	764		
Units: Participants	78	103		

Statistical analyses

Statistical analysis title	COVID-19 Day 14: Regardless Baseline

Statistical analysis description:

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by age and household size.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0205
Method	Miettinen & Nurminen method
Parameter estimate	Confidence Interval
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-0.1

Secondary: Percentage of Participants Who Had Undetectable SARS-CoV-2 in Baseline NP Swabs and Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection With Symptoms) Through Day 29

End point title	Percentage of Participants Who Had Undetectable SARS-CoV-2 in Baseline NP Swabs and Developed COVID-19 (Laboratory-Confirmed SARS-CoV-2 Infection With Symptoms) Through Day 29

End point description:

Participants who experienced targeted symptoms of COVID-19 (e.g., cough, sore throat) and had NP swabs tested for SARS-CoV-2 using RT-PCR. The efficacy analysis population was the mITT (modified intent to treat) population consisting of all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Day 29

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	630	634		
Units: Participants	51	65		

Statistical analyses

Statistical analysis title	COVID-19 at Day 29 With no SARS-CoV-2 at Baseline

Statistical analysis description:

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by age and household size.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	1264
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Miettinen & Nurminen method
Parameter estimate	Confidence Interval
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	1

Notes:

[3] - Adjusted differences and the corresponding confidence intervals.

Secondary: Percentage of Participants Who Had Undetectable SARS-CoV-2 in Baseline NP Swabs and Developed Detectable SARS-CoV-2 in NP Swabs on or Before Day 14

End point title	Percentage of Participants Who Had Undetectable SARS-CoV-2 in Baseline NP Swabs and Developed Detectable SARS-CoV-2 in NP Swabs on or Before Day 14

End point description:

All participants had NP swabs collected at screening and through Day 14 to test for SARS-CoV-2 using RT-PCR. Efficacy analysis was conducted on the mITT (modified intent to treat) population consisting of all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	572	589		
Units: Participants	65	85		

Statistical analyses

Statistical analysis title	SARS-CoV-2 RNA at Day 14: No Baseline SARS-CoV-2.

Statistical analysis description:

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by age and household size.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	1161
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Confidence Interval
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	0.8

Notes:

[4] - Adjusted differences and the corresponding confidence intervals

Secondary: Percentage of Participants who had Detectable SARS-CoV-2 in Baseline NP Swabs and Developed COVID-19 (laboratory-confirmed SARS-CoV-2 Infection With Symptoms) Through Day 14

End point title	Percentage of Participants who had Detectable SARS-CoV-2 in Baseline NP Swabs and Developed COVID-19 (laboratory-confirmed SARS-CoV-2 Infection With Symptoms) Through Day 14

End point description:

Participants who experienced targeted symptoms of COVID-19 (e.g., cough, sore throat) and had NP swabs tested for SARS-CoV-2 using RT-PCR. Efficacy analysis was conducted on the mITT (modified intent to treat) population consisting of all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Molnupiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Participants	35	47		

Statistical analyses

Statistical analysis title	COVID-19 at Day 14 With SARS-CoV-2 in Baseline.

Statistical analysis description:

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by age and household size.

Comparison groups	Molnupiravir v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other[5]
Method	Miettinen & Nurminen method
Parameter estimate	Mean difference (final values)
Point estimate	-10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	2

Notes:

[5] - Adjusted differences and the corresponding confidence intervals.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to Day 29

Adverse event reporting additional description:

Safety Analyses was conducted in all-participants-as-treated (APaT) population, which consisted of all randomized participants who received at least 1 dose of study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	MK-4482
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported

Serious adverse events	Placebo	MK-4482	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 765 (0.26%)	3 / 763 (0.39%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 765 (0.00%)	1 / 763 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 765 (0.13%)	0 / 763 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 765 (0.13%)	2 / 763 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	MK-4482	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 765 (0.00%)	0 / 763 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2021	The key reasons for this amendment were to 1) make the evaluation of laboratory-confirmed COVID-19 through Day 14 in participants with undetectable SARS-CoV-2 in baseline nasopharyngeal (NP) swabs a key secondary endpoint; 2) align the windows (5-days) for COVID-19 symptoms and SARS-CoV-2 testing in the index; and 3) to collect symptom diaries in all participants through Day 29.
28 January 2022	The primary rationale for this amendment was to revise the primary efficacy objective to include only those participants with undetectable SARS-CoV-2 in baseline nasopharyngeal swabs, and to update the interim analysis to include an assessment of early efficacy. These changes required an increase in the sample size (from 1332 to 1500) and an update of the timing of the interim analysis.
09 May 2022	The rationale for this amendment is 1) to add as a secondary objective and associated hypothesis for the prevention of laboratory-confirmed COVID-19 through Day 14 in participants regardless of SARS-CoV-2 results (detectable or undetectable) in baseline NP swabs, and 2) to align male contraception requirements across the study with the requirements in the US EUA Fact Sheet for MOV even if not required locally.
21 June 2022	The rationale for this amendment is 1) to update the interim analysis to remove the assessment of early efficacy; only safety and futility will be assessed at the interim analysis 2) to revise the power calculation and sample size as a result of removing the assessment of early efficacy at the interim analysis and 3) to correct errors mistakenly introduced in the prior amendment in the third secondary objective and second exploratory objective.
16 November 2022	The rationale for this amendment is 1) to update the anti-SARS-CoV-2 neutralizing antibody testing method and 2) to allow use of qualitative OP swab data, under extenuating circumstances where NP swab data are not available, for baseline viral status categorization (ie, to establish whether they are in the primary analysis population, mITT-VN) and for clinical outcome assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37690669