



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 | v2 (current) |
| This version publication date | 02 June 2024 |
| First version publication date | 22 November 2023 |
| Version creation reason | |

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 | EudraCT: 2021-000904-39, jRCT (Japan Registry of Clinical Trials): jRCT2031210281, 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: 15 |
| Country: Number of subjects enrolled | Brazil: 12 |
| Country: Number of subjects enrolled | Bulgaria: 114 |
| Country: Number of subjects enrolled | Colombia: 322 |
| Country: Number of subjects enrolled | Egypt: 111 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Guatemala: 36 |
| Country: Number of subjects enrolled | Hungary: 19 |
| Country: Number of subjects enrolled | Japan: 42 |
| Country: Number of subjects enrolled | Kenya: 11 |
| Country: Number of subjects enrolled | Mexico: 234 |
| Country: Number of subjects enrolled | Philippines: 33 |
| Country: Number of subjects enrolled | Romania: 66 |
| Country: Number of subjects enrolled | Russian Federation: 279 |
| Country: Number of subjects enrolled | South Africa: 201 |
| Country: Number of subjects enrolled | Thailand: 16 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Türkiye: 10 |
| Country: Number of subjects enrolled | Ukraine: 262 |
| Country: Number of subjects enrolled | United States: 656 |
| Worldwide total number of subjects | 2441 |
| EEA total number of subjects | 201 |

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) | 37 |
| Adolescents (12-17 years) | 39 |
| Adults (18-64 years) | 2163 |
| From 65 to 84 years | 193 |
| 85 years and over | 9 |

Subject disposition

Recruitment

Recruitment details:

Only eligible participants without confirmed or suspected coronavirus disease 2019 (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 were enrolled but not randomized to receive study treatment. Besides baseline characteristics and some optional swab collection, no other data was gathered. Survival and mortality data for index cases was not collected per protocol, neither was data collected for protocol specified outcome measures.

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.

| | |
|------------------|--------------------|
| Arm title | Index Participants |
|------------------|--------------------|

Arm description:

Index case was a participant with documented COVID-19 infection. Index participants were enrolled but did not receive study intervention. Index participants resided in the same household as enrolled participants who received study intervention.

| | |
|-----------------------------------------------------------|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Molnupiravir | Placebo | Index Participants |
|-----------------------------------------------|--------------|---------|--------------------|
| Started | 768 | 771 | 902 |
| Treated | 763 | 765 | 0 |
| Completed | 750 | 751 | 0 |
| Not completed | 18 | 20 | 902 |
| Consent withdrawn by subject | 10 | 11 | - |
| Physician decision | 1 | - | - |
| Randomized By Mistake Without Study Treatment | 1 | - | - |
| Death | - | 1 | - |
| Lost to follow-up | - | 5 | - |
| Discontinued per protocol | - | - | 902 |
| 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 title | Index Participants |
| Reporting group description: | |
| Index case was a participant with documented COVID-19 infection. Index participants were enrolled but did not receive study intervention. Index participants resided in the same household as enrolled participants who received study intervention. | |

| Reporting group values | Molnupiravir | Placebo | Index Participants |
|----------------------------------------------------|--------------|---------|--------------------|
| Number of subjects | 768 | 771 | 902 |
| 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 | 37 |
| Adolescents (12-17 years) | 0 | 0 | 39 |
| Adults (18-64 years) | 707 | 709 | 747 |
| From 65-84 years | 57 | 59 | 77 |
| 85 years and over | 4 | 3 | 2 |
| Age Continuous Units: years | | | |
| median | 37.0 | 37.0 | 38.0 |
| standard deviation | ± 15.6 | ± 15.5 | ± 17.7 |
| Gender Categorical Units: Subjects | | | |
| Female | 366 | 342 | 541 |
| Male | 402 | 429 | 361 |
| Race Units: Subjects | | | |
| American Indian Or Alaska Native | 85 | 90 | 80 |
| Asian | 48 | 40 | 62 |
| Black Or African American | 62 | 60 | 77 |
| Native Hawaiian Or Other Pacific Islander | 1 | 4 | 2 |
| White | 453 | 446 | 552 |
| Multiple | 119 | 129 | 128 |
| Missing | 0 | 2 | 1 |
| Ethnicity Units: Subjects | | | |

| | | | |
|------------------------------------------------------------------------------------------------|-----|-----|-----|
| Hispanic Or Latino | 323 | 340 | 341 |
| Not Hispanic Or Latino | 445 | 430 | 552 |
| Not Reported | 0 | 1 | 9 |
| Stratification Factor at Randomization Collected via IRT: Household Size Units: Subjects | | | |
| <=3 | 269 | 271 | 0 |
| >=3 | 499 | 500 | 0 |
| No Data Collected | 0 | 0 | 902 |
| Stratification Factor at Randomization Collected via IRT: Age Group Units: Subjects | | | |
| <=60 | 680 | 680 | 0 |
| >=60 | 88 | 91 | 0 |
| No Data Collected | 0 | 0 | 902 |

| | | | |
|----------------------------------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 2441 | | |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 37 | | |
| Adolescents (12-17 years) | 39 | | |
| Adults (18-64 years) | 2163 | | |
| From 65-84 years | 193 | | |
| 85 years and over | 9 | | |
| Age Continuous Units: years median standard deviation | - | | |
| Gender Categorical Units: Subjects | | | |
| Female | 1249 | | |
| Male | 1192 | | |
| Race Units: Subjects | | | |
| American Indian Or Alaska Native | 255 | | |
| Asian | 150 | | |
| Black Or African American | 199 | | |
| Native Hawaiian Or Other Pacific Islander | 7 | | |
| White | 1451 | | |
| Multiple | 376 | | |
| Missing | 3 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic Or Latino | 1004 | | |
| Not Hispanic Or Latino | 1427 | | |

| | | | |
|------------------------------------------------------------------------------------------------|------|--|--|
| Not Reported | 10 | | |
| Stratification Factor at Randomization Collected via IRT: Household Size Units: Subjects | | | |
| <=3 | 540 | | |
| >=3 | 999 | | |
| No Data Collected | 902 | | |
| Stratification Factor at Randomization Collected via IRT: Age Group Units: Subjects | | | |
| <=60 | 1360 | | |
| >=60 | 179 | | |
| No Data Collected | 902 | | |

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. | |
| Reporting group title | Index Participants |
| Reporting group description: Index case was a participant with documented COVID-19 infection. Index participants were enrolled but did not receive study intervention. Index participants resided in the same household as enrolled participants who received study intervention. | |

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 ^[1] |
| 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 were reported. 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. Index participants were not included in OM analysis per protocol. | |
| End point type | Primary |
| End point timeframe: Day 14 | |
| Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistical analysis was not done for this endpoint | |

| 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 With ≥ 1 Adverse Event

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title | Percentage of Participants With ≥ 1 Adverse Event ^[2] |
| 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. Index participants were not included in OM analysis per protocol. | |
| End point type | Primary |
| End point timeframe: | |
| 29 days | |
| Notes: | |
| [2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistical analysis was not done for this endpoint | |

| 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 ^[3] |
| 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:

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

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

| | |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Discontinuing From Study Therapy due to AE ^[4] |
|-----------------|--------------------------------------------------------------------------------------|

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. Index participants were not included in OM analysis per protocol.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 5 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not done for this endpoint

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| 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 ^[5] |
| 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:

[5] - 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 ^[6] |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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. Index participants were not included in OM analysis per protocol.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 14

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not done for this endpoint

| 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 ^[7] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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. Index participants were not included in OM analysis per protocol.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 29

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not done for this endpoint

| 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 ^[8] |
| 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:

[8] - 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 ^[9] |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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. Index participants were not included in OM analysis per protocol.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to Day 14 | |

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this endpoint

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| 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 ^[10] |
| Parameter estimate | Confidence Interval |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 0.8 |

Notes:

[10] - 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 ^[11] |
| 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. Index participants were not included in OM analysis per protocol. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Day 14 | |

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not done for this endpoint

| 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 ^[12] |
| 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:

[12] - 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:

All cause mortality (ACM) was analyzed in all randomized participants. 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. Per protocol all-cause mortality and AE information was not collected for index cases.

| | |
|-----------------|------------|
| 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: There were no non-serious adverse events reported during this study.

| 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>