# Clinical trial results:
# A Study to Assess the Effect of MK-7264 (AF-219) on Cough Reflex Sensitivity in Both Healthy and Chronic Cough Subjects

## Summary

| | |
|---|---|
| EudraCT number | 2015-002034-47 |
| Trial protocol | GB |
| Global end of trial date | 20 October 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 01 November 2017 |
| First version publication date | 01 November 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MK-7264-014 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02476890 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IP Name: MK-7264, IP Name: AF-219 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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 | 20 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 October 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of a single dose of 100 mg MK-7264 on cough reflex sensitivity to various challenge agents (capsaicin, citric acid, adenosine triphosphate [ATP], and distilled water) in both healthy and chronic cough participants. Cough challenge agents were administered in random order for each participant at Baseline (Day 0), and repeated in the same order at subsequent visits.

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 participants involved in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 28 October 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 36 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 36 |

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) | 24 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The main purpose of the 6-day Screening period (Day -6 to Day -1) was to ensure that each participant met all the specified eligibility criteria. In addition, cough reflex sensitivity was measured at Screening by standard clinical methodology using cough challenge in response to 4 agents (capsaicin, citric acid, ATP, and distilled water).

### Period 1

| | |
|---|---|
| Period 1 title | Period 1 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo then MK-7264 100 mg/Healthy (Sequence A) |

Arm description:

Healthy participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 1

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 2

| | |
|---|---|
| **Arm title** | MK-7264 100 mg then placebo/Healthy (Sequence B) |

Arm description:

Healthy participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 1

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 2

| | |
|---|---|
| **Arm title** | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |

Arm description:

Chronic Cough participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 1

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 2

| | |
|---|---|
| **Arm title** | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |

Arm description:

Chronic Cough participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 2

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 1

| Number of subjects in period 1 | Placebo then MK-7264 100 mg/Healthy (Sequence A) | MK-7264 100 mg then placebo/Healthy (Sequence B) | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |
|---|---|---|---|
| Started | 6 | 6 | 12 |
| Completed | 6 | 6 | 12 |

| Number of subjects in period 1 | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |
|---|---|
| Started | 12 |
| Completed | 12 |

| **Period 2** | |
|---|---|
| Period 2 title | Period 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

| **Arms** | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo then MK-7264 100 mg/Healthy (Sequence A) |

Arm description:

Healthy participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 2

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 1

| | |
|---|---|
| **Arm title** | MK-7264 100 mg then placebo/Healthy (Sequence B) |

Arm description:

Healthy participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between

Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 2

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 1

| | |
|---|---|
| **Arm title** | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |

Arm description:

Chronic Cough participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 1

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 2

| | |
|---|---|
| **Arm title** | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |

Arm description:

Chronic Cough participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo, administered as a single dose in treatment Period 2

| | |
|---|---|
| Investigational medicinal product name | MK-7264 100 mg |
| Investigational medicinal product code | |
| Other name | AF-219 |

| | |
|---|---|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MK-7264 100 mg (2 x 50 mg), administered as a single dose in treatment Period 1

| **Number of subjects in period 2** | Placebo then MK-7264 100 mg/Healthy (Sequence A) | MK-7264 100 mg then placebo/Healthy (Sequence B) | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |
|---|---|---|---|
| Started | 6 | 6 | 12 |
| Completed | 6 | 6 | 12 |

| **Number of subjects in period 2** | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |
|---|---|
| Started | 12 |
| Completed | 12 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Period 1 |
| Reporting group description: | |
| All participants who were randomised in the study | |

| Reporting group values | Period 1 | Total | |
|---|---|---|---|
| Number of subjects | 36 | 36 | |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 24 | 24 | |
| From 65-84 years | 12 | 12 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 53.3 | | |
| standard deviation | ± 14.0 | - | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 32 | 32 | |
| Male | 4 | 4 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo then MK-7264 100 mg/Healthy (Sequence A) |
| Reporting group description: | |
| Healthy participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | MK-7264 100 mg then placebo/Healthy (Sequence B) |
| Reporting group description: | |
| Healthy participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |
| Reporting group description: | |
| Chronic Cough participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |
| Reporting group description: | |
| Chronic Cough participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | Placebo then MK-7264 100 mg/Healthy (Sequence A) |
| Reporting group description: | |
| Healthy participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | MK-7264 100 mg then placebo/Healthy (Sequence B) |
| Reporting group description: | |
| Healthy participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | Placebo then MK-7264 100 mg/Chronic Cough (Sequence A) |
| Reporting group description: | |
| Chronic Cough participants in Sequence A received a single dose of placebo in treatment Period 1 then a single dose of MK-7264 100 mg in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Reporting group title | MK-7264 100 mg then placebo/Chronic Cough (Sequence B) |
| Reporting group description: | |
| Chronic Cough participants in Sequence B received a single dose of MK-7264 100 mg in treatment Period 1 then a single dose of placebo in treatment Period 2. There was a minimum 48-hr washout between Periods 1 & 2. | |
| Subject analysis set title | MK-7264 100 mg/Healthy |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Healthy participants received MK-7264 100 mg in two treatment sequences and were administered cough challenge agents (capsaicin, citric acid, ATP, and distilled water) in random order at Baseline (Day 0), and repeated in the same order at subsequent visits 1 hour post-morning dose. | |
| Subject analysis set title | Placebo/Healthy |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Healthy participants received placebo in two treatment sequences and were administered cough challenge agents (capsaicin, citric acid, ATP, and distilled water) in random order at Baseline (Day 0), and repeated in the same order at subsequent visits 1 hour post-morning dose. | |
| Subject analysis set title | MK-7264 100 mg/Chronic Cough |

| | |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Chronic Cough participants received MK-7264 100 mg in two treatment sequences and were administered cough challenge agent (capsaicin, citric acid, ATP, and distilled water) in random order at Baseline (Day 0), and repeated in the same order at subsequent visits 1 hour post-morning dose.

| | |
|---|---|
| Subject analysis set title | Placebo/Chronic Cough |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Chronic Cough participants received placebo in two treatment sequences and were administered cough challenge agents (capsaicin, citric acid, ATP, and distilled water) in random order at Baseline (Day 0), and repeated in the same order at subsequent visits 1 hour post-morning dose.

## Primary: Cough Reflex Sensitivity to Capsaicin in Participants Who Received MK-7264 100 mg and Placebo

| | |
|---|---|
| End point title | Cough Reflex Sensitivity to Capsaicin in Participants Who Received MK-7264 100 mg and Placebo |

End point description:

The concentration of capsaicin inducing at least 2 coughs (C2) and 5 coughs (C5), each averaged across 3 time points (at 1, 3, and 5 hours post-dose), on the treatment days were assessed in healthy and chronic cough participants who received a single dose of MK-7264 or placebo in Periods 1 & 2 combined. The concentrations of capsaicin for cough challenge ranged from 0.3-1000 µM. The challenge agent was prepared by dilution of a stock solution of capsaicin with saline. A mixed effects model used natural log-transformed values for the lowest concentrations of inhaled solution required to evoke at least 2 (C2) or 5 (C5) coughs. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of cough reflex sensitivity in response to capsaicin challenge.

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

End point timeframe:

5 hours

| **End point values** | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: µM | | | | |
| least squares mean (confidence interval 95%) | | | | |
| C2 Response to Capsaicin (Periods 1 & 2) | 3.05 (2.6 to 3.5) | 3.04 (2.6 to 3.5) | 1.72 (1.3 to 2.1) | 1.41 (1.0 to 1.8) |
| C5 Response to Capsaicin (Periods 1 & 2) | 4.46 (3.9 to 5.0) | 4.68 (4.1 to 5.3) | 2.31 (1.9 to 2.8) | 2.05 (1.6 to 2.5) |

## Statistical analyses

| **Statistical analysis title** | MMRM Analysis: C2 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a mixed effect repeated measures (MMRM) model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |

| | |
|---|---|
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.9666 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.7 |

Notes:

[1] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM Analysis: C5 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | = 0.5993 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.6 |

Notes:

[2] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM Analysis: C2 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | = 0.2823 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.32 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.9 |

Notes:

[3] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

| **Statistical analysis title** | MMRM Analysis: C5 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a mixed effect repeated measures (MMRM) model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| P-value | = 0.4287 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.9 |

Notes:

[4] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

## Primary: Cough Reflex Sensitivity to Citric Acid in Participants Who Received MK-7264 100 mg and Placebo

| | |
|---|---|
| End point title | Cough Reflex Sensitivity to Citric Acid in Participants Who Received MK-7264 100 mg and Placebo |

End point description:

The concentration of citric acid inducing at least 2 coughs (C2) and 5 coughs (C5), each averaged across 3 time points (at 1, 3, and 5 hours post-dose), on the treatment days were assessed in healthy and chronic cough participants who received a single dose of MK-7264 or placebo in Periods 1 & 2 combined. The concentrations of citric acid for cough challenge ranged from 1 mM-3M. The challenge agent was prepared by dilution of a stock solution of citric acid with saline. A mixed effects model used natural log-transformed values for the lowest concentrations of inhaled solution required to evoke at least 2 (C2) or 5 (C5) coughs. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of cough reflex sensitivity in response to citric acid challenge.

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

End point timeframe:

5 hours

| End point values | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: mM | | | | |
| least squares mean (confidence interval 95%) | | | | |
| C2 Response to Citric Acid (Periods 1 & 2) | 6.16 (5.6 to 6.8) | 5.61 (5.0 to 6.2) | 4.07 (3.6 to 4.6) | 3.84 (3.3 to 4.3) |
| C5 Response to Citric Acid (Periods 1 & 2) | 7.12 (6.4 to 7.6) | 6.82 (6.1 to 7.6) | 4.74 (4.2 to 5.2) | 4.46 (4.0 to 5.0) |

## Statistical analyses

| Statistical analysis title | MMRM Analysis: C2 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| P-value | = 0.1771 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 1.4 |

Notes:

[5] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| Statistical analysis title | MMRM Analysis: C5 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | = 0.5473 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.3 |

Notes:

[6] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM Analysis: C2 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | = 0.5169 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 1 |

Notes:

[7] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

| **Statistical analysis title** | MMRM Analysis: C5 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[8] |
| P-value | = 0.4243 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1 |

Notes:

[8] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

## Primary: Cough Reflex Sensitivity to ATP in Participants Who Received MK-7264 100

| mg and Placebo | |
|---|---|
| End point title | Cough Reflex Sensitivity to ATP in Participants Who Received MK-7264 100 mg and Placebo |

End point description:

The concentration of ATP inducing at least 2 coughs (C2) and 5 coughs (C5), each averaged across 3 time points (at 1, 3, and 5 hours post-dose), on the treatment days were assessed in healthy and chronic cough participants who received a single dose of MK-7264 or placebo in Periods 1 & 2 combined. The concentrations of ATP for cough challenge ranged from 0.1 mM-300 mM. The challenge agent was prepared by dilution of a stock solution of ATP with saline. A mixed effects model used natural log-transformed values for the lowest concentrations of inhaled solution required to evoke at least 2 (C2) or 5 (C5) coughs. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of cough reflex sensitivity in response to ATP challenge.

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

End point timeframe:

5 hours

| End point values | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: mM | | | | |
| least squares mean (confidence interval 95%) | | | | |
| C2 Response to ATP (Periods 1 & 2) | 4.79 (4.0 to 5.6) | 3.90 (3.1 to 4.7) | 2.90 (2.3 to 3.5) | 1.36 (0.8 to 2.0) |
| C5 Response to ATP (Periods 1 & 2) | 5.61 (5.3 to 5.9) | 4.73 (4.3 to 5.1) | 3.52 (2.9 to 4.2) | 2.22 (1.6 to 2.9) |

## Statistical analyses

| Statistical analysis title | MMRM Analysis: C2 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
|---|---|
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[9] |
| P-value | = 0.1125 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 2 |

Notes:

[9] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM Analysis: C5 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[10] |
| P-value | = 0.0029 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 1.4 |

Notes:

[10] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM Analysis: C2 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | = 0.0006 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 2.4 |

Notes:

[11] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

| **Statistical analysis title** | MMRM Analysis: C5 Response (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |

| | |
|---|---|
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[12] |
| P-value | = 0.0067 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 2.2 |

Notes:

[12] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

## Primary: Cough Reflex Sensitivity to Distilled Water in Participants Who Received MK-7264 100 mg and Placebo

| | |
|---|---|
| End point title | Cough Reflex Sensitivity to Distilled Water in Participants Who Received MK-7264 100 mg and Placebo |

End point description:

The concentration of distilled water inducing at least 2 coughs (C2) and 5 coughs (C5), each averaged across 3 time points (at 1, 3, and 5 hours post-dose), on the treatment days were assessed in healthy and chronic cough participants who received a single dose of MK-7264 or placebo in Periods 1 & 2 combined. The concentrations of distilled water for cough challenge ranged from 20%-100%. The challenge agent was prepared by dilution of distilled water with saline. A mixed effects model used natural log-transformed values for the lowest concentrations of inhaled solution required to evoke at least 2 (C2) or 5 (C5) coughs. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of cough reflex sensitivity in response to distilled water challenge.

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

End point timeframe:

5 hours

| **End point values** | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: % concentration | | | | |
| least squares mean (confidence interval 95%) | | | | |
| C2 Response to Distilled Water(Periods 1 & 2) | 4.72 (4.6 to 4.8) | 4.34 (4.2 to 4.4) | 4.42 (4.3 to 4.5) | 4.12 (4.0 to 4.2) |
| C5 Response to Distilled Water(Periods 1 & 2) | 4.85 (4.6 to 5.1) | 4.61 (4.4 to 4.8) | 4.51 (4.4 to 4.6) | 4.24 (4.1 to 4.4) |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | MMRM: C2 Reponse (Healthy) |

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[13] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.5 |

Notes:

[13] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM: C5 Response (Healthy) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a MMRM model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Healthy v Placebo/Healthy |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other[14] |
| P-value | = 0.1798 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.6 |

Notes:

[14] - This was a crossover study, and the same number of healthy participants (n=12) received two comparative treatments. As such, 12 participants were analysed, not 24 participants.

| **Statistical analysis title** | MMRM: C2 Reponse (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a mixed effect repeated measures (MMRM) model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |

| | |
|---|---|
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | = 0.0011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 0.5 |

Notes:

[15] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

| **Statistical analysis title** | MMRM: C5 Reponse (Chronic Cough) |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a mixed effect repeated measures (MMRM) model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[16] |
| P-value | = 0.0023 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 0.4 |

Notes:

[16] - This was a crossover study, and the same number of chronic cough participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

## Secondary: Change From Baseline in Cough Severity VAS After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only)

| End point title | Change From Baseline in Cough Severity VAS After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only) |
|---|---|

End point description:

Chronic cough participants completed a visual analogue scale (VAS) prior to dosing on the treatment day in each treatment period, and one hour after the final cough challenge on the treatment days. Participants used a 100mm VAS scale of cough severity from 'No Cough' (0) up to 'Worst Cough' (100). They were instructed to draw a line on the scale to indicate how severe they felt their cough was during the previous 1 hour on the treatment days. The analysed population was all treated chronic cough participants who had at least 1 post-dose primary endpoint assessment of cough severity VAS.

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

End point timeframe:

1 day

| End point values | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: Scores on a scale | | | | |
| least squares mean (confidence interval 95%) | -26.2 (-36.2 to -16.2) | -8.2 (-18.7 to 2.2) | | |

## Statistical analyses

| Statistical analysis title | Cough Severity VAS Analysis |
|---|---|

Statistical analysis description:

Treatment comparison was performed using a mixed effect repeated measures (MMRM) model that includes fixed effects for period, treatment group, and all interaction terms of treatment, timepoint, and period, and the baseline value (on the log scale) as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[17] |
| P-value | = 0.0037 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.8 |
| upper limit | -6.2 |

Notes:

[17] - This was a crossover study, and the same number of participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

## Secondary: Change From Baseline in Urge to Cough VAS After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only)

| End point title | Change From Baseline in Urge to Cough VAS After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only) |
|---|---|

End point description:

Chronic cough participants completed a VAS prior to dosing on the treatment day in each treatment period, and one hour after the final cough challenge on the treatment days. Participants used a 100mm scale to record the severity of their urge to cough but marked at the extremes as 'No urge-to-cough' (0) and 'Worst urge-to-cough' (100). They were instructed to draw a single vertical line on the scale to indicate how severe their urge to cough was during the previous 1 hour on the treatment days. The analysed population was all treated chronic cough participants who had at least 1 post-dose primary endpoint assessment of urge to cough VAS.

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

End point timeframe:

1 day

| End point values | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: Scores on a scale | | | | |
| least squares mean (confidence interval 95%) | -29.8 (-38.9 to -20.7) | -11.7 (-20.9 to -2.6) | | |

### Statistical analyses

| Statistical analysis title | Urge to Cough VAS Analysis |
|---|---|

Statistical analysis description:

The mixed effect model included fixed effects for treatment group, period, the treatment-by-period interaction, and the Baseline value as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[18] |
| P-value | = 0.002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.1 |
| upper limit | -7 |

Notes:

[18] - This was a crossover study, and the same number of participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

### Secondary: Change From Baseline in Cough Frequency After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only)

| End point title | Change From Baseline in Cough Frequency After Cough Challenge Testing in Participants Who Received MK-7264 100 mg and Placebo (Chronic Cough Participants Only) |
|---|---|

End point description:

An ambulatory cough recording device was attached to chronic cough participants. The device recorded all sounds the participant made during cough monitoring (from post-cough challenge to approximately 24 hours later). The resulting recording was processed by validated custom written software which determined the total number of coughs and coughs per hour. The change from Baseline in objective cough frequency was measured on the treatment days. The analysed population was all treated chronic cough participants who had at least 1 post-dose primary endpoint assessment of cough frequency.

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

End point timeframe:

24 hours

| End point values | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 24 | 24 | | |
| Units: Counts/hr | | | | |
| least squares mean (confidence interval 95%) | -7.7 (-10.1 to -5.3) | -4.1 (-6.5 to -1.7) | | |

### Statistical analyses

| Statistical analysis title | Cough Frequency Analysis |
|---|---|

Statistical analysis description:

The mixed effect model included fixed effects for treatment group, period, the treatment-by-period interaction, and the Baseline value as a covariate.

| | |
|---|---|
| Comparison groups | MK-7264 100 mg/Chronic Cough v Placebo/Chronic Cough |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other[19] |
| P-value | = 0.0075 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.2 |
| upper limit | -1 |

Notes:

[19] - This was a crossover study, and the same number of participants (n=24) received two comparative treatments. As such, 24 participants were analysed, not 48 participants.

### Secondary: Percentage of Participants Who Experienced One or More Adverse Events During Study Treatment and Follow up

| End point title | Percentage of Participants Who Experienced One or More Adverse Events During Study Treatment and Follow up |
|---|---|

End point description:

A secondary endpoint of the trial was the percentage of participants receiving MK-7264 100 mg or placebo who had at least 1 adverse event (AE) during the treatment periods (including washout periods) in addition to 14 days (+3 days) until a post-treatment follow-up visit. The relative number (n/N [%]) of participants in any treatment group with at least 1 AE was assessed for days 1-18. The analysed population was all randomised participants who took at least 1 dose of study treatment and had assessment of AE occurrence.

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

End point timeframe:

18 days

| End point values | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 100.0 | 50.0 | 95.8 | 33.3 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event

| End point title | Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event |
|---|---|

End point description:

A secondary endpoint of the trial was the percentage of participants receiving MK-7264 100 mg or placebo who discontinued treatment due to an AE. The relative number (n/N [%]) of participants who discontinued treatment due to an AE. The analysed population was all randomised participants who took at least 1 dose of study treatment and had assessment of discontinuation due to an AE.

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

End point timeframe:

4 days

| End point values | MK-7264 100 mg/Healthy | Placebo/Healthy | MK-7264 100 mg/Chronic Cough | Placebo/Chronic Cough |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 24 | 24 |
| Units: Percentge of participants | 0 | 0 | 0 | 0 |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| 18 days | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

| Reporting groups | |
|---|---|
| Reporting group title | MK-7264 100 mg/Healthy |
| Reporting group description: - | |
| Reporting group title | Placebo /Healthy |
| Reporting group description: - | |
| Reporting group title | MK-7264 100 mg/Chronic Cough |
| Reporting group description: - | |
| Reporting group title | Placebo/Chronic Cough |
| Reporting group description: - | |

| Serious adverse events | MK-7264 100 mg/Healthy | Placebo /Healthy | MK-7264 100 mg/Chronic Cough |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Placebo/Chronic Cough | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | MK-7264 100 mg/Healthy | Placebo /Healthy | MK-7264 100 mg/Chronic Cough |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 6 / 12 (50.00%) | 21 / 24 (87.50%) |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 1 / 12 (8.33%) | 7 / 24 (29.17%) |
| occurrences (all) | 6 | 1 | 7 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Dysgeusia | | | |
| subjects affected / exposed | 9 / 12 (75.00%) | 1 / 12 (8.33%) | 16 / 24 (66.67%) |
| occurrences (all) | 9 | 1 | 16 |
| Headache | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 12 (25.00%) | 6 / 24 (25.00%) |
| occurrences (all) | 0 | 3 | 6 |
| Hypogeusia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 0 / 12 (0.00%) | 6 / 24 (25.00%) |
| occurrences (all) | 4 | 0 | 6 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 4 / 24 (16.67%) |
| occurrences (all) | 3 | 0 | 6 |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Oral disorder | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 2 | 0 | 1 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 12 (8.33%) | 4 / 24 (16.67%) |
| occurrences (all) | 1 | 1 | 6 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dry throat | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngeal disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngeal hypoaesthesia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| **Non-serious adverse events** | Placebo/Chronic Cough | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |

| | | | |
|---|---|---|---|
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Hypogeusia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Oral disorder | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dry throat | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal disorder | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal hypoaesthesia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 September 2015 | Study treatment (AF-219) was changed from "100 mg BID, administered as two 50 mg tablets BID" to "100 mg, administered as two 50 mg tablets". |
| 19 April 2016 | A screening procedure was amended (i. e., spirometry in healthy participants only), and exclusion criteria for cough were clarified. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported