



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
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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)
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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)
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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)
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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)
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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
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Reporting group description:

All participants who were randomised in the study

Reporting group values	Period 1	Total	
Number of subjects	36	36	
Age Categorical			
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			
Units: years			
arithmetic mean	53.3		
standard deviation	± 14.0	-	
Gender Categorical			
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)
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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)
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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)
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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
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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
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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)
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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)
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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)
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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)
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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
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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
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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)
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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
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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
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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)
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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)
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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)
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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
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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)
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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)
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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
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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)
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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)
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	MK-7264 100 mg/Healthy
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Reporting group description: -

Reporting group title	Placebo /Healthy
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Reporting group description: -

Reporting group title	MK-7264 100 mg/Chronic Cough
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Reporting group description: -

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

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