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

Summary

EudraCT number	2015-000464-34
Trial protocol	GB
Global end of trial date	16 May 2016

Results information

Result version number	v1
This version publication date	31 May 2017
First version publication date	31 May 2017

Trial information

Trial identification

Sponsor protocol code	7264-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02397460
WHO universal trial number (UTN)	-

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	16 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2016
Global end of trial reached?	Yes
Global end of trial date	16 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of single doses of AF-219 300 mg (Cohort 1) and 50 mg (Cohort 2) on cough reflex sensitivity to capsaicin in both healthy and chronic cough subjects.

Protection of trial subjects:

The Investigators agreed to conduct the study in compliance with the study Protocol, with the International Standard of Good Clinical Practice (GCP) procedures, with all applicable local GCP standards and regulations, and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	42
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The main purpose of the 14-day Screening period (Day -14 to Day -1) was to ensure that each participant met all the specified eligibility criteria. In addition, cough sensitivity was measured at Screening by standard clinical methodology using cough challenge in response to capsaicin.

Period 1

Period 1 title	Treatment 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	AF-219 300 mg/Healthy (Sequence A)

Arm description:

Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 300 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AF-219 300 mg (6 x 50 mg), administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4

Arm title	AF-219 300 mg /Healthy (Sequence B)

Arm description:

Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence A)

Arm description:

Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence B)

Arm description:

Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 50 mg/Healthy (Sequence A)

Arm description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 50 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
AF-219 50 mg, administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4	
Arm title	AF-219 50 mg /Healthy (Sequence B)
Arm description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence A)
Arm description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence B)
Arm description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	AF-219 300 mg/Healthy (Sequence A)	AF-219 300 mg /Healthy (Sequence B)	AF-219 300 mg/Chronic Cough (Sequence A)
Started	7	7	6
Completed	7	7	6

Number of subjects in period 1	AF-219 300 mg/Chronic Cough (Sequence B)	AF-219 50 mg/Healthy (Sequence A)	AF-219 50 mg /Healthy (Sequence B)
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1	AF-219 50 mg/Chronic Cough (Sequence A)	AF-219 50 mg/Chronic Cough (Sequence B)
Started	6	6
Completed	6	6

Period 2

Period 2 title	Treatment 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	AF-219 300 mg/Healthy (Sequence A)

Arm description:

Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 300 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AF-219 300 mg (6 x 50 mg), administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4

Arm title	AF-219 300 mg /Healthy (Sequence B)

Arm description:

Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence A)

Arm description:

Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence B)

Arm description:

Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 50 mg/Healthy (Sequence A)

Arm description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 50 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
AF-219 50 mg, administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4	
Arm title	AF-219 50 mg /Healthy (Sequence B)
Arm description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence A)
Arm description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence B)
Arm description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	AF-219 300 mg/Healthy (Sequence A)	AF-219 300 mg /Healthy (Sequence B)	AF-219 300 mg/Chronic Cough (Sequence A)
Started	7	7	6
Completed	7	7	6
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 2	AF-219 300 mg/Chronic Cough (Sequence B)	AF-219 50 mg/Healthy (Sequence A)	AF-219 50 mg /Healthy (Sequence B)
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 2	AF-219 50 mg/Chronic Cough (Sequence A)	AF-219 50 mg/Chronic Cough (Sequence B)
Started	6	6

Completed	6	5
Not completed	0	1
Adverse event, non-fatal	-	1

Period 3

Period 3 title	Treatment Period 3
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	AF-219 300 mg/Healthy (Sequence A)

Arm description:

Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 300 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AF-219 300 mg (6 x 50 mg), administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4

Arm title	AF-219 300 mg /Healthy (Sequence B)

Arm description:

Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence A)

Arm description:

Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence B)

Arm description:

Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 50 mg/Healthy (Sequence A)

Arm description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 50 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
AF-219 50 mg, administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4	
Arm title	AF-219 50 mg /Healthy (Sequence B)
Arm description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence A)
Arm description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence B)
Arm description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	AF-219 300 mg/Healthy (Sequence A)	AF-219 300 mg /Healthy (Sequence B)	AF-219 300 mg/Chronic Cough (Sequence A)
Started	7	7	6
Completed	7	7	6

Number of subjects in period 3	AF-219 300 mg/Chronic Cough (Sequence B)	AF-219 50 mg/Healthy (Sequence A)	AF-219 50 mg /Healthy (Sequence B)
Started	6	6	6
Completed	6	6	6

Number of subjects in period 3	AF-219 50 mg/Chronic Cough (Sequence A)	AF-219 50 mg/Chronic Cough (Sequence B)
Started	6	5
Completed	6	5

Period 4

Period 4 title	Treatment Period 4
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	AF-219 300 mg/Healthy (Sequence A)

Arm description:

Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 300 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AF-219 300 mg (6 x 50 mg), administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4

Arm title	AF-219 300 mg /Healthy (Sequence B)

Arm description:

Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence A)

Arm description:

Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 300 mg/Chronic Cough (Sequence B)

Arm description:

Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4

Arm type	AF-219 300 mg in Pd. 1 & 3, placebo in Pd. 2 & 4

No investigational medicinal product assigned in this arm

Arm title	AF-219 50 mg/Healthy (Sequence A)

Arm description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
Investigational medicinal product name	AF-219 50 mg
Investigational medicinal product code	AF-219
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
AF-219 50 mg, administered as a single dose, with crossover to/from placebo in treatment Period 1 through treatment Period 4	
Arm title	AF-219 50 mg /Healthy (Sequence B)
Arm description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence A)
Arm description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	
Arm title	AF-219 50 mg/Chronic Cough (Sequence B)
Arm description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Arm type	AF-219 50 mg in Pd. 1 & 3, placebo in Pd. 2 & 4
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	AF-219 300 mg/Healthy (Sequence A)	AF-219 300 mg /Healthy (Sequence B)	AF-219 300 mg/Chronic Cough (Sequence A)
Started	7	7	6
Completed	7	6	6
Not completed	0	1	0
Physician decision	-	-	-
Adverse event, non-fatal	-	1	-

Number of subjects in period 4	AF-219 300 mg/Chronic Cough (Sequence B)	AF-219 50 mg/Healthy (Sequence A)	AF-219 50 mg /Healthy (Sequence B)
Started	6	6	5
Completed	6	5	5
Not completed	0	1	0
Physician decision	-	1	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 4	AF-219 50 mg/Chronic Cough (Sequence A)	AF-219 50 mg/Chronic Cough (Sequence B)
Started	6	6
Completed	6	6
Not completed	0	0
Physician decision	-	-
Adverse event, non-fatal	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1

Reporting group description: -

Reporting group values	Treatment Period 1	Total	
Number of subjects	50	50	
Age Categorical			
Participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2)			
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)	42	42	
From 65-84 years	8	8	
85 years and over	0	0	
Age Continuous			
Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2)			
Units: years			
arithmetic mean	42.7		
standard deviation	± 14.2	-	
Gender Categorical			
Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2)			
Units: Subjects			
Female	19	19	
Male	31	31	

End points

End points reporting groups

Reporting group title	AF-219 300 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	

Reporting group title	AF-219 50 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	
Reporting group title	AF-219 300 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 300 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 300 mg in Periods 1 & 3	

Reporting group title	AF-219 300 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 300 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Healthy (Sequence A)
Reporting group description:	
Healthy participants received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg /Healthy (Sequence B)
Reporting group description:	
Healthy participants received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence A)
Reporting group description:	
Participants with chronic cough received placebo, had a 2-week washout, and then switched to AF-219 50 mg in Periods 1 & 3	
Reporting group title	AF-219 50 mg/Chronic Cough (Sequence B)
Reporting group description:	
Participants with chronic cough received AF-219 50 mg, had a 2-week washout, and then switched to placebo in Periods 2 & 4	
Subject analysis set title	Healthy Males, Placebo: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males who received placebo and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough Males, Placebo: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Males with chronic cough who received placebo and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough Females, Placebo: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Females with chronic cough who received placebo and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy Males, AF-219: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males who received AF-219 (300 mg or 50 mg) and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough Males, AF-219: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Males with chronic cough who received AF-219 (300 mg or 50 mg) and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough Females, AF-219: Capsaicin
Subject analysis set type	Full analysis
Subject analysis set description:	
Females with chronic cough who received AF-219 (300 mg or 50 mg) and had capsaicin-evoked cough challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy Males, Placebo: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males who received placebo and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy Males, AF-219 50 mg: ATP

Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males who received AF-219 50 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Males, Placebo: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Males with chronic cough who received placebo and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Males, AF-219 50 mg: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Males with chronic cough who received AF-219 50 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Females, Placebo: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Females with chronic cough who received placebo and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Females, AF-219 50 mg: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Females with chronic cough who received AF-219 50 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy Males, AF-219 300 mg: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males who received AF-219 300 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Males, AF-219 300 mg: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Males with chronic cough who received AF-219 300 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough Females, AF-219 300 mg: ATP
Subject analysis set type	Full analysis
Subject analysis set description:	
Females with chronic cough who received AF-219 300 mg and had ATP-evoked cough challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/AF-219 300 mg: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 300 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/Placebo: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 1 who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/AF-219 300 mg: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 300 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/Placebo: Capsaicin (C2)

Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 1 with chronic cough who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/AF-219 50 mg: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 50 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/Placebo: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 2 who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/AF-219 50 mg: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 50 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/Placebo: Capsaicin (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough in Cohort 2 who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/AF-219 300 mg: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 300 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/Placebo: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 1 who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/AF-219 300 mg: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 300 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/Placebo: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 1 with chronic cough who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/AF-219 50 mg: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 50 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/Placebo: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 2 who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/AF-219 50 mg: Capsaicin (C5)

Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 50 mg and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Chronic Cough/Placebo: Capsaicin (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 2 with chronic cough who received placebo and had capsaicin challenge 2 hours post-dose in Periods 1 & 2	
Subject analysis set title	Healthy/AF-219 300 mg: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 300 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/Placebo: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 1 who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/AF-219 300 mg: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 300 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/Placebo: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 1 with chronic cough who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/AF-219 50 mg: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 50 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/Placebo: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 2 who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/AF-219 50 mg: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 50 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/Placebo: ATP (C2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough in Cohort 2 who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/AF-219 300 mg: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 300 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/Placebo: ATP (C5)

Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 1 who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/AF-219 300 mg: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 300 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/Placebo: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 1 with chronic cough who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/AF-219 50 mg: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females who received AF-219 50 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Healthy/Placebo: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Healthy males and females in Cohort 2 who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/AF-219 50 mg: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females with chronic cough who received AF-219 50 mg and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	Chronic Cough/Placebo: ATP (C5)
Subject analysis set type	Full analysis
Subject analysis set description:	
Males and females in Cohort 2 with chronic cough who received placebo and had ATP challenge 2 hours post-dose in Periods 3 & 4	
Subject analysis set title	AF-219 300 mg Cough: Capsaicin (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (AF-219 300 mg) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: Capsaicin (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (placebo) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	AF-219 300 mg Cough: Capsaicin (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (AF-219 300 mg) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: Capsaicin (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (placebo) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	AF-219 50 mg Cough: Capsaicin (Day 1)

Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (AF-219 50 mg) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: Capsaicin (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (Placebo) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	AF-219 50 mg Cough: Capsaicin (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (AF-219 50 mg) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: Capsaicin (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (placebo) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	AF-219 300 mg Cough: ATP (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (AF-219 300 mg) who recorded their urge-to-cough on Day 1, 4 hours post-dose following ATP challenge	
Subject analysis set title	Placebo Cough: ATP (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (Placebo) who recorded their urge-to-cough on Day 1, 4 hours post-dose following ATP challenge	
Subject analysis set title	AF-219 300 mg Cough: ATP (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (AF-219 300 mg) who recorded their urge-to-cough on Day 2, 24 hours post-dose following ATP challenge	
Subject analysis set title	Placebo Cough: ATP (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 1 (Placebo) who recorded their urge-to-cough on Day 2, 24 hours post-dose following ATP challenge	
Subject analysis set title	AF-219 50 mg Cough: ATP (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (AF-219 50 mg) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: ATP (Day 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (Placebo) who recorded their urge-to-cough on Day 1, 4 hours post-dose following capsaicin challenge	
Subject analysis set title	AF-219 50 mg Cough: ATP (Day 2)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (AF-219 50 mg) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	Placebo Cough: ATP (Day 2)

Subject analysis set type	Full analysis
Subject analysis set description:	
Participants in Cohort 2 (Placebo) who recorded their urge-to-cough on Day 2, 24 hours post-dose following capsaicin challenge	
Subject analysis set title	Healthy Participants: AF-219 300 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Healthy Participants: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Chronic Cough Participants: AF-219 300 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Chronic Cough Participants: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Healthy Participants: AF-219 50 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Healthy Participants: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Chronic Cough Participants: AF-219 50 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Chronic Cough Participants: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	
Subject analysis set title	Chronic Cough Participants: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with adverse events	

Primary: Cough Reflex Sensitivity to Capsaicin Measured by Maximal Cough Response (Emax) in Healthy and Chronic Cough Participants (Males and Females)

End point title	Cough Reflex Sensitivity to Capsaicin Measured by Maximal Cough Response (Emax) in Healthy and Chronic Cough Participants (Males and Females)

End point description:

A co-primary objective was to assess the effect of single doses of 300 mg and 50 mg AF-219 on cough reflex sensitivity to challenge with capsaicin in both healthy participants and participants with chronic cough. Capsaicin-evoked cough challenge was performed 2 hours post-dose in Periods 1 & 2. The maximal cough response (Emax) to capsaicin was assessed. For capsaicin challenge doubling concentrations from 0.49-1000 µM were prepared by dilution of stock solutions with saline. The number of explosive cough sounds occurring within the first 15 seconds after inhalation are recorded. Nonlinear mixed-effects modeling was used to estimate the Emax. Population pharmacodynamic modelling was performed in NONMEM 7.3. Data exploration, goodness-of-fit plots, statistical analyses, and simulations

were performed in Matlab R2015a. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of Emax in response to capsaicin challenge.

End point type	Primary

End point timeframe:

2 hours post-dose

End point values	Healthy Males, Placebo: Capsaicin	Chronic Cough Males, Placebo: Capsaicin	Chronic Cough Females, Placebo: Capsaicin	Healthy Males, AF-219: Capsaicin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14[1]	3	10	14
Units: Emax (Explosive coughs/15 sec)				
number (not applicable)	4.14	4.14	7.55	3.66

Notes:

[1] - All of the values presented in this table are model-based.

End point values	Chronic Cough Males, AF-219: Capsaicin	Chronic Cough Females, AF-219: Capsaicin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	10		
Units: Emax (Explosive coughs/15 sec)				
number (not applicable)	3.37	6.15		

Statistical analyses

Statistical analysis title	Emax Response: AF-219 v Placebo

Statistical analysis description:

Treatment effects on Emax following capsaicin challenge were modeled for dose dependence and were estimated on the basis of disease status for participants who were healthy or had chronic cough and received AF-219 300 mg, AF-219 50 mg, or placebo.

Comparison groups	Healthy Males, Placebo: Capsaicin v Chronic Cough Males, Placebo: Capsaicin v Chronic Cough Females, Placebo: Capsaicin v Healthy Males, AF-219: Capsaicin v Chronic Cough Males, AF-219: Capsaicin v Chronic Cough Females, AF-219: Capsaicin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Primary: Cough Reflex Sensitivity to Capsaicin Measured by the Tussive Concentration Required to Achieve 50% of Emax (E50) in Healthy and Chronic Cough Participants (Males and Females)

End point title	Cough Reflex Sensitivity to Capsaicin Measured by the Tussive

	Concentration Required to Achieve 50% of Emax (E50) in Healthy and Chronic Cough Participants (Males and Females)

End point description:

A co-primary objective was to assess the effect of single doses of 300 mg and 50 mg AF-219 on cough reflex sensitivity to challenge with capsaicin in both healthy participants and participants with chronic cough (CC). Capsaicin-evoked cough challenge was performed 2 hours post-dose in Periods 1 & 2. The concentration of capsaicin required to induce 50% of the Emax (ED50) was assessed. For capsaicin challenge doubling concentrations from 0.49-1000 µM were prepared by dilution of stock solutions with saline. Nonlinear mixed-effects modeling was used to estimate the ED50. Population pharmacodynamic modelling was performed in NONMEM 7.3 using Laplace estimation method. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. The analysed population was all treated participants who had at least 1 post-dose primary endpoint assessment of ED50 in response to capsaicin challenge.

End point type	Primary

End point timeframe:

2 hours post-dose

End point values	Healthy Males, Placebo: Capsaicin	Chronic Cough Males, Placebo: Capsaicin	Chronic Cough Females, Placebo: Capsaicin	Healthy Males, AF-219: Capsaicin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14[2]	3	10	14
Units: µM				
number (not applicable)	33	33	9.57	33

Notes:

[2] - All of the values presented in this table are model-based.

End point values	Chronic Cough Males, AF-219: Capsaicin	Chronic Cough Females, AF-219: Capsaicin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	10		
Units: µM				
number (not applicable)	33	9.57		

Statistical analyses

Statistical analysis title	ED50 Response: AF-219 v Placebo

Statistical analysis description:

Treatment effects following capsaicin challenge were modeled for dose dependence and were estimated on
the basis of disease status for participants who had chronic cough and received AF-219 300 mg, AF-219 50 mg, or placebo.

Comparison groups	Chronic Cough Males, Placebo: Capsaicin v Chronic Cough Females, Placebo: Capsaicin v Chronic Cough Males, AF-219: Capsaicin v Chronic Cough Females, AF-219: Capsaicin

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Secondary: Cough Reflex Sensitivity to Adenosine Triphosphate (ATP) Measured by Maximal Cough Response (Emax) in Healthy and Chronic Cough Participants (Males and Females)

End point title	Cough Reflex Sensitivity to Adenosine Triphosphate (ATP) Measured by Maximal Cough Response (Emax) in Healthy and Chronic Cough Participants (Males and Females)

End point description:

A secondary objective was to assess the effect of single doses of 300 mg and 50 mg AF-219 on cough reflex sensitivity to challenge with adenosine triphosphate (ATP) in both healthy participants and participants with chronic cough. ATP-evoked cough challenge was performed 2 hours post-dose in Periods 3 & 4. For ATP challenge doubling concentrations from 0.227 to 929 µmol/mL were prepared from ATP powder dissolved in saline. The number of explosive cough sounds occurring within the first 15 seconds after inhalation are recorded. Nonlinear mixed-effects modeling was used to estimate the Emax. Population pharmacodynamic modelling was performed in NONMEM 7.3. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of Emax in response to ATP challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy Males, Placebo: ATP	Healthy Males, AF-219 50 mg: ATP	Chronic Cough Males, Placebo: ATP	Chronic Cough Males, AF-219 50 mg: ATP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14[3]	14	3	3
Units: Emax (Explosive coughs/15 sec)				
number (not applicable)	2.35	2.35	2.35	2.35

Notes:

[3] - All of the values presented in this table are model-based.

End point values	Chronic Cough Females, Placebo: ATP	Chronic Cough Females, AF-219 50 mg: ATP	Healthy Males, AF-219 300 mg: ATP	Chronic Cough Males, AF-219 300 mg: ATP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	14	3
Units: Emax (Explosive coughs/15 sec)				
number (not applicable)	5.41	5.41	2.35	2.35

End point values	Chronic Cough Females, AF-			

	219 300 mg: ATP			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Emax (Explosive coughs/15 sec)				
number (not applicable)	5.41			

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Reflex Sensitivity to ATP Measured by the Tussive Concentration Required to Achieve 50% of Emax (E50) in Healthy and Chronic Cough Participants (Males and Females)

End point title	Cough Reflex Sensitivity to ATP Measured by the Tussive Concentration Required to Achieve 50% of Emax (E50) in Healthy and Chronic Cough Participants (Males and Females)

End point description:

A secondary objective was to assess the effect of single doses of 300 mg and 50 mg AF-219 on cough reflex sensitivity to challenge with ATP in both healthy participants and participants with chronic cough. ATP-evoked cough challenge was performed 2 hours post-dose in Periods 3 & 4. The concentration of capsaicin required to induce 50% of the Emax (ED50) was assessed. For capsaicin challenge doubling concentrations from 0.227-929 µmol/mL were prepared by dilution of stock solutions with saline. Nonlinear mixed-effects modeling was used to estimate the ED50. Population pharmacodynamic modelling was performed in NONMEM 7.3 using Laplace estimation method. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of ED50 in response to ATP challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy Males, Placebo: ATP	Healthy Males, AF-219 50 mg: ATP	Chronic Cough Males, Placebo: ATP	Chronic Cough Males, AF-219 50 mg: ATP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14[4]	14	3	3
Units: µmol/mL				
number (not applicable)	54.9	119.13	54.9	155.92

Notes:

[4] - All of the values presented in this table are model-based.

End point values	Chronic Cough Females, Placebo: ATP	Chronic Cough Females, AF-219 50 mg: ATP	Healthy Males, AF-219 300 mg: ATP	Chronic Cough Males, AF-219 300 mg: ATP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	14	3
Units: µmol/mL				
number (not applicable)	8.62	24.48	119.13	192.7

End point values	Chronic Cough Females, AF-219 300 mg: ATP			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: µmol/mL				
number (not applicable)	30.25			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Capsaicin Inducing 2 or More Coughs (C2)

End point title	Concentrations of Capsaicin Inducing 2 or More Coughs (C2)

End point description:

The concentrations of capsaicin inducing 2 or more coughs (C2) were assessed in treatment Periods 1 & 2 combined. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of C2 in response to capsaicin challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy/AF-219 300 mg: Capsaicin (C2)	Healthy/Placebo: Capsaicin (C2)	Chronic Cough/AF-219 300 mg: Capsaicin (C2)	Chronic Cough/Placebo: Capsaicin (C2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	14	10	10
Units: µM				
median (full range (min-max))	31.25 (4 to 1000)	31.25 (4 to 500)	3.9 (0 to 16)	7.81 (0 to 31)

End point values	Healthy/AF-219 50 mg: Capsaicin (C2)	Healthy/Placebo: Capsaicin (C2)	Chronic Cough/AF-219 50 mg: Capsaicin (C2)	Chronic Cough/Placebo: Capsaicin (C2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	10	12
Units: µM				
median (full range (min-max))	15.62 (2 to 63)	23.44 (8 to 125)	15.62 (0 to 125)	5.86 (0 to 250)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Capsaicin Inducing 5 or More Coughs (C5)

End point title	Concentrations of Capsaicin Inducing 5 or More Coughs (C5)

End point description:

The concentrations of capsaicin inducing 5 or more coughs (C5) were assessed in treatment Periods 1 & 2 combined. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of C5 in response to capsaicin challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy/AF-219 300 mg: Capsaicin (C5)	Healthy/Placebo: Capsaicin (C5)	Chronic Cough/AF-219 300 mg: Capsaicin (C5)	Chronic Cough/Placebo: Capsaicin (C5)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	6	10	10
Units: µM				
median (full range (min-max))	31.25 (16 to 250)	62.5 (16 to 1000)	3.9 (0 to 31)	11.72 (0 to 125)

End point values	Healthy/AF-219 50 mg: Capsaicin (C5)	Healthy/Placebo: Capsaicin (C5)	Chronic Cough/AF-219 50 mg: Capsaicin (C5)	Chronic Cough/Placebo: Capsaicin (C5)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	7	7	10
Units: µM				
median (full range (min-max))	250 (63 to 500)	125 (63 to 500)	15.62 (2 to 63)	5.86 (0 to 31)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of ATP Inducing 2 or More Coughs (C2)

End point title	Concentrations of ATP Inducing 2 or More Coughs (C2)

End point description:

The concentrations of ATP inducing 2 or more coughs (C2) were assessed in treatment Periods 3 & 4 combined. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of C2 in response to ATP challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy/AF-219 300 mg: ATP (C2)	Healthy/Placebo: ATP (C2)	Chronic Cough/AF-219 300 mg: ATP (C2)	Chronic Cough/Placebo: ATP (C2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	11	7	11
Units: mg/mL				
median (full range (min-max))	192 (8 to 256)	64 (1 to 512)	8 (0 to 64)	1 (0 to 64)

End point values	Healthy/AF-219 50 mg: ATP (C2)	Healthy/Placebo: ATP (C2)	Chronic Cough/AF-219 50 mg: ATP (C2)	Chronic Cough/Placebo: ATP (C2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	8	8	9
Units: mg/mL				
median (full range (min-max))	16 (8 to 256)	24 (2 to 512)	4.25 (0 to 512)	4 (0 to 256)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of ATP Inducing 5 or More Coughs (C5)

End point title	Concentrations of ATP Inducing 5 or More Coughs (C5)

End point description:

The concentrations of ATP inducing 5 or more coughs (C5) were assessed in treatment Periods 3 & 4 combined. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of C5 in response to ATP challenge.

End point type	Secondary

End point timeframe:

2 hours post-dose

End point values	Healthy/AF-219 300 mg: ATP (C5)	Healthy/Placebo: ATP (C5)	Chronic Cough/AF-219 300 mg: ATP (C5)	Chronic Cough/Placebo: ATP (C5)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	5	7	8
Units: mg/mL				
median (full range (min-max))	192 (128 to 256)	128 (64 to 256)	8 (0 to 64)	16.5 (0 to 512)

End point values	Healthy/AF-219 50 mg: ATP (C5)	Healthy/Placebo: ATP (C5)	Chronic Cough/AF-219 50 mg: ATP (C5)	Chronic Cough/Placebo: ATP (C5)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	5	8
Units: mg/mL				
median (full range (min-max))	64 (32 to 256)	32 (2 to 32)	128 (8 to 512)	4 (0 to 128)

Statistical analyses

No statistical analyses for this end point

Secondary: Urge-to-Cough in Response to Capsaicin Challenge (Chronic Cough Participants)

End point title	Urge-to-Cough in Response to Capsaicin Challenge (Chronic Cough Participants)

End point description:

In response to capsaicin challenge in Periods 1 & 2 (combined), participants with chronic cough completed a visual analogue scale (VAS) at the end of each 4-hour observation period on Day 1, and 24 hours after each observation period, on Day 2. Participants used a 100mm VAS to record the severity of their urge to cough marked at the extremes as 'No urge-to-cough' (0 mm) and 'Worst urge-to-cough' (100 mm). They drew a single vertical line on the VAS to indicate how severe their urge to cough was during the previous 4 hours on Day 1 of each Treatment Period, and during the previous 24 hours (Day 2 of each Treatment Period). The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of urge-to-cough in response to capsaicin challenge.

End point type	Secondary

End point timeframe:

4 hours and 24 hours post-dose

End point values	AF-219 300 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)	AF-219 300 mg Cough: Capsaicin (Day 2)	Placebo Cough: Capsaicin (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mm				
arithmetic mean (standard deviation)	28.9 (± 29.79)	38.6 (± 26.82)	28.2 (± 32.72)	46.7 (± 29.2)

End point values	AF-219 50 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)	AF-219 50 mg Cough: Capsaicin (Day 2)	Placebo Cough: Capsaicin (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	11	12	11
Units: mm				
arithmetic mean (standard deviation)	36.6 (± 30.84)	20.5 (± 11.54)	41.8 (± 31.02)	36.7 (± 23.28)

Statistical analyses

No statistical analyses for this end point

Secondary: Urge-to-Cough in Response to ATP Challenge (Chronic Cough Participants)

End point title	Urge-to-Cough in Response to ATP Challenge (Chronic Cough Participants)

End point description:

In response to ATP challenge in Periods 3 & 4 (combined), participants with chronic cough completed a VAS at the end of each 4-hour observation period on Day 1, and 24 hours after each observation period, on Day 2. Participants used a 100mm VAS to record the severity of their urge to cough marked at the extremes as 'No urge-to-cough' (0 mm) and 'Worst urge-to-cough' (100 mm). They drew a single vertical line on the VAS to indicate how severe their urge to cough was during the previous 4 hours on Day 1 of each Treatment Period, and during the previous 24 hours (Day 2 of each Treatment Period). The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of urge-to-cough in response to ATP challenge.

End point type	Secondary

End point timeframe:

4 hours and 24 hours post-dose

End point values	AF-219 300 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)	AF-219 300 mg Cough: ATP (Day 2)	Placebo Cough: ATP (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mm				
arithmetic mean (standard deviation)	19.8 (± 23.54)	34.4 (± 26.78)	21.6 (± 20.65)	39.8 (± 26.51)

End point values	AF-219 50 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)	AF-219 50 mg Cough: ATP (Day 2)	Placebo Cough: ATP (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
arithmetic mean (standard deviation)	21.5 (± 22.45)	25.3 (± 19.69)	27.5 (± 29.54)	37.5 (± 27.33)

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity in Response to Capsaicin Challenge (Chronic Cough Participants)

End point title	Cough Severity in Response to Capsaicin Challenge (Chronic Cough Participants)

End point description:

In response to capsaicin challenge in Periods 1 & 2 (combined), participants with chronic cough completed a VAS at the end of each 4-hour observation period on Day 1, and 24 hours after each observation period, on Day 2. Participants used a 100mm VAS to record their cough severity marked at the extremes as 'No Cough' (0 mm) and 'Worst Cough' (100 mm). They drew a single vertical line on the VAS to indicate how severe their urge to cough was during the previous 4 hours on Day 1 of each Treatment Period, and during the previous 24 hours (Day 2 of each Treatment Period). The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of cough severity in response to capsaicin challenge.

End point type	Secondary

End point timeframe:

4 hours and 24 hours post-dose

End point values	AF-219 300 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)	AF-219 300 mg Cough: Capsaicin (Day 2)	Placebo Cough: Capsaicin (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mm				
arithmetic mean (standard deviation)	28.2 (± 30.71)	35.7 (± 24.32)	25.8 (± 30.2)	44.3 (± 27.43)

End point values	AF-219 50 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)	AF-219 50 mg Cough: Capsaicin (Day 2)	Placebo Cough: Capsaicin (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	11	12	11
Units: mm				
arithmetic mean (standard deviation)	30.9 (± 27.22)	20.5 (± 12.75)	39.8 (± 28.97)	35.5 (± 22.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity in Response to ATP Challenge (Chronic Cough Participants)

End point title	Cough Severity in Response to ATP Challenge (Chronic Cough Participants)

End point description:

In response to ATP challenge in Periods 3 & 4 (combined), participants with chronic cough completed a VAS at the end of each 4-hour observation period on Day 1, and 24 hours after each observation period, on Day 2. Participants used a 100mm VAS to record their cough severity marked at the extremes as 'No Cough' (0 mm) and 'Worst Cough' (100 mm). They drew a single vertical line on the VAS to indicate how severe their urge to cough was during the previous 4 hours on Day 1 of each Treatment Period, and during the previous 24 hours (Day 2 of each Treatment Period). The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of cough severity in response to ATP challenge.

End point type	Secondary

End point timeframe:

4 hours and 24 hours post-dose

End point values	AF-219 300 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)	AF-219 300 mg Cough: ATP (Day 2)	Placebo Cough: ATP (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mm				
arithmetic mean (standard deviation)	21.5 (± 27.06)	32.7 (± 24.23)	18.9 (± 18.29)	36.8 (± 26.5)

End point values	AF-219 50 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)	AF-219 50 mg Cough: ATP (Day 2)	Placebo Cough: ATP (Day 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
arithmetic mean (standard deviation)	21.2 (± 21.04)	23.5 (± 16.02)	27.5 (± 26.78)	35.5 (± 24.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Daytime Cough Frequency in Participants With Chronic Cough Who Underwent Capsaicin Challenge

End point title	Daytime Cough Frequency in Participants With Chronic Cough Who Underwent Capsaicin Challenge

End point description:

Daily cough frequency monitoring was performed in participants with chronic cough, who were attached to a digital sound recorder with 2 microphones (a lapel air microphone attached to the participant's clothing and an adhesive chest wall microphone attached to the skin at the top of the sternum). Participants wore the sound recorder from the start of capsaicin challenge to bedtime on Day 1 in

treatment Periods 1 & 2. The resulting recording was processed by software which cut out the majority of speech and background noise but retained cough sounds. The investigator listened to the recording and documented the number of coughs per hour. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of daytime cough frequency in response to capsaicin challenge.

End point type	Secondary

End point timeframe:

From start of challenge (2 hours post-dose) to bedtime; Up to 12 hours

End point values	AF-219 300 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)	AF-219 50 mg Cough: Capsaicin (Day 1)	Placebo Cough: Capsaicin (Day 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: coughs/hour				
arithmetic mean (standard deviation)	13.7 (± 13.85)	19.1 (± 16.76)	15.5 (± 16.92)	20.3 (± 13.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Daytime Cough Frequency in Participants With Chronic Cough Who Underwent ATP Challenge

End point title	Daytime Cough Frequency in Participants With Chronic Cough Who Underwent ATP Challenge

End point description:

Daily cough frequency monitoring was performed in participants with chronic cough, who were attached to a digital sound recorder with 2 microphones (a lapel air microphone attached to the participant's clothing and an adhesive chest wall microphone attached to the skin at the top of the sternum). Participants wore the sound recorder from the start of ATP challenge to bedtime on Day 1 in treatment Periods 3 & 4. The resulting recording was processed by software which cut out the majority of speech and background noise but retained cough sounds. The investigator listened to the recording and documented the number of coughs per hour. The analysed population was all treated participants who had at least 1 post-dose secondary endpoint assessment of daytime cough frequency in response to ATP challenge.

End point type	Secondary

End point timeframe:

From start of challenge (2 hours post-dose) to bedtime; Up to 12 hours

End point values	AF-219 300 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)	AF-219 50 mg Cough: ATP (Day 1)	Placebo Cough: ATP (Day 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	11	11
Units: coughs/hour				
arithmetic mean (standard deviation)	10.3 (± 11.65)	22.3 (± 15.48)	15.6 (± 17.31)	26.4 (± 16.75)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced at Least One Adverse Event (AE) During Treatment and Post-treatment Follow-up

End point title	Percentage of Participants Who Experienced at Least One Adverse Event (AE) During Treatment and Post-treatment Follow-up

End point description:

A secondary endpoint of the trial was the percentage of participants receiving MK-7264 at any dose (300 mg or 50 mg) who had at least 1 AE over 24 days of treatment (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 1-41. The analysed population was all randomized participants who took at least 1 dose of study treatment and had assessment of AE occurrence.

End point type	Secondary

End point timeframe:

Up to Day 41

End point values	Healthy Participants: AF-219 300 mg	Healthy Participants: Placebo	Chronic Cough Participants: AF-219 300 mg	Chronic Cough Participants: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	14	12	12
Units: Percentage of Participants				
number (not applicable)	100	35.7	100	58.3

End point values	Healthy Participants: AF-219 50 mg	Healthy Participants: Placebo	Chronic Cough Participants: AF-219 50 mg	Chronic Cough Participants: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	11
Units: Percentage of Participants				
number (not applicable)	75	33.3	50	27.3

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 at any dose (300 mg or 50 mg) who discontinued treatment due to an AE. The relative number (n/N [%]) of participants who discontinued treatment due to AEs was assessed for days 1-24. The analysed population was all randomized 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:

Up to Day 24

End point values	Healthy Participants: AF-219 300 mg	Chronic Cough Participants: AF-219 300 mg	Healthy Participants: AF-219 50 mg	Chronic Cough Participants: AF-219 50 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	12	12	12
Units: Percentage of participants				
number (not applicable)	7.1	0	8.3	8.3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Day 41	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Cohort 1-Healthy Subjects: AF-219 300 mg
Reporting group description: -	
Reporting group title	Cohort 1-Healthy Subjects: Placebo
Reporting group description: -	
Reporting group title	Cohort 1-Chronic Cough Subjects: AF-219 300 mg
Reporting group description: -	
Reporting group title	Cohort 1-Chronic Cough Subjects: Placebo
Reporting group description: -	
Reporting group title	Cohort 2-Healthy Subjects: AF-219 50 mg
Reporting group description: -	
Reporting group title	Cohort 2-Healthy Subjects: Placebo
Reporting group description: -	
Reporting group title	Cohort 2-Chronic Cough Subjects: AF-219 50 mg
Reporting group description: -	
Reporting group title	Cohort 2-Chronic Cough Subjects: Placebo
Reporting group description: -	

Serious adverse events	Cohort 1-Healthy Subjects: AF-219 300 mg	Cohort 1-Healthy Subjects: Placebo	Cohort 1-Chronic Cough Subjects: AF-219 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 1-Chronic Cough Subjects: Placebo	Cohort 2-Healthy Subjects: AF-219 50 mg	Cohort 2-Healthy Subjects: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 2-Chronic Cough Subjects: AF-219 50 mg	Cohort 2-Chronic Cough Subjects: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Cohort 1-Healthy Subjects: AF-219 300 mg	Cohort 1-Healthy Subjects: Placebo	Cohort 1-Chronic Cough Subjects: AF-219 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	5 / 14 (35.71%)	12 / 12 (100.00%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Excoriation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	4
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			

subjects affected / exposed	13 / 14 (92.86%)	1 / 14 (7.14%)	9 / 12 (75.00%)
occurrences (all)	20	1	15
Headache			
subjects affected / exposed	3 / 14 (21.43%)	2 / 14 (14.29%)	5 / 12 (41.67%)
occurrences (all)	3	2	5
Hypogeusia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	3
VIIth Nerve Paralysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypoaesthesia oral			

subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Paraesthesia oral			
subjects affected / exposed	4 / 14 (28.57%)	0 / 14 (0.00%)	4 / 12 (33.33%)
occurrences (all)	4	0	4
Reflux gastritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tongue coated			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tooth deposit			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry throat			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Oropharyngeal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oropharyngeal pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pharyngeal hypoaesthesia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Throat irritation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Oral herpes			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 1-Chronic Cough Subjects: Placebo	Cohort 2-Healthy Subjects: AF-219 50 mg	Cohort 2-Healthy Subjects: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	9 / 12 (75.00%)	4 / 12 (33.33%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Excoriation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 12 (33.33%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 12 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Headache			

subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Hypogeusia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
VIIth Nerve Paralysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Reflux gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tongue coated			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth deposit			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	3 / 12 (25.00%)
occurrences (all)	0	2	3
Dry throat			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Pharyngeal hypoaesthesia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 2-Chronic Cough Subjects: AF-219 50 mg	Cohort 2-Chronic Cough Subjects: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	3 / 11 (27.27%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Excoriation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 11 (9.09%)	
occurrences (all)	5	1	
Headache			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Hypogeusia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
VIIth Nerve Paralysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Paraesthesia oral			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Reflux gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Salivary hypersecretion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Tongue coated			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Tooth deposit			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 12 (25.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Dry throat			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oropharyngeal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Pharyngeal hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Throat irritation			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Spinal osteoarthritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2015	Added steps specifying when and for which treatment group the cough monitor was attached and removed
17 July 2015	Clarified that an ambulatory cough recorder chest microphone (in addition to the lapel microphone) would be used for cough participants only
05 August 2015	Removed spirometry from the Schedule of Assessments and Procedures
02 September 2015	Low Dose Extension (AF-219 50 mg, Cohort 2) added to include up to an additional 24 participants
19 October 2015	Time frame of the exclusion criteria for treatment with an investigational drug decreased to facilitate the enrollment of participants in Cohort 1 into Cohort 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported