



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 |

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 |
|-----------------|---|

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

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 occurrences (all) | 13 / 14 (92.86%) 20 | 1 / 14 (7.14%) 1 | 9 / 12 (75.00%) 15 |
| Headache subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 2 / 14 (14.29%) 2 | 5 / 12 (41.67%) 5 |
| Hypogeusia subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 0 / 14 (0.00%) 0 | 3 / 12 (25.00%) 3 |
| VIIth Nerve Paralysis subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 14 (0.00%) 0 | 1 / 12 (8.33%) 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 occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 12 (16.67%) 2 | 1 / 12 (8.33%) 1 |
| Hypogeusia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 12 (0.00%) 0 |
| VIIth Nerve Paralysis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hypoaesthesia oral subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 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 occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Wheezing subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Spinal osteoarthritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Oral herpes subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 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 occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Excoriation subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Vascular disorders | | | |
| Hot flush subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Nervous system disorders | | | |
| Ageusia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 5 | 1 / 11 (9.09%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 11 (18.18%) 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 occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Wheezing subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Spinal osteoarthritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 11 (0.00%) 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