Clinical trial results:
A Randomised, Double-Blind, Double-Dummy, Placebo-Controlled, Three-Way Cross-over Study to Evaluate the Effect of AF-219 on Methacholine Hyper-reactivity in Subjects with Asthma

Summary

EudraCT number	2013-003566-13
Trial protocol	GB
Global end of trial date	15 March 2015

Results information

Result version number	v2 (current)
This version publication date	10 April 2021
First version publication date	30 December 2016
Version creation reason	• Correction of full data set Update for consistency with ClinicalTrials.gov Results posting

Trial information

Trial identification

Sponsor protocol code	AF219-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01993329
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-7264-009

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	28 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2014
Global end of trial reached?	Yes
Global end of trial date	15 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the PC20 response (concentration of methacholine required to cause at least a 20% fall in lung function) of two dose levels of AF-219 compared with placebo in participants with asthma after provocation with methacholine.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure defined for this individual study was in place for the protection of trial subjects: allowed prior and concomitant medications were short acting inhaled β2-agonists (SABA) administered as rescue medication. A minimum period of 8 hours was to elapse between the use of rescue (SABA) and spirometry measurements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2013
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

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)	20

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

20 participants were enrolled, randomized and treated.

Pre-assignment

Screening details:

A Screening Phase of up to 21 days ensured that each participant met all the specified inclusion and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Arm description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

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

Dosage and administration details:

Gefapixant at 50 mg BID for 4 days

Arm title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Arm description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details: Matching placebo to mimic gefapixant 300 mg BID for 4 days	
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Gefapixant at 50 mg BID for 4 days	
Arm title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Arm description: Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Arm type	Experimental
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Gefapixant at 300 mg BID for 4 days	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo to mimic gefapixant 50 mg BID for 4 days	
Arm title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg
Arm description: Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Arm type	Experimental
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Gefapixant at 300 mg BID for 4 days	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo to mimic gefapixant 50 mg BID for 4 days	
Arm title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

Arm title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

Number of subjects in period 1	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Started	3	4	3
Completed	3	4	3

Number of subjects in period 1	Gefapixant 300 mg>Placebo>Gefapi	Placebo> Gefapixant 50 mg>Gefapixant	Placebo> Gefapixant 300 mg>Gefapixant

	xant 50 mg	300 mg	50 mg
Started	3	3	4
Completed	3	3	4

Period 2

Period 2 title	Wash-out
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Arm description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Arm description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Started	3	4	3
Completed	3	4	3

Number of subjects in period 2	Gefapixant 300 mg>Placebo>Gefapixant 50 mg	Placebo> Gefapixant 50 mg>Gefapixant 300 mg	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Started	3	3	4
Completed	3	3	4

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Arm description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	Experimental

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Gefapixant at 300 mg BID for 4 days

Arm title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Arm description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

Arm title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Gefapixant at 50 mg BID for 4 days

Arm title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

Arm title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

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

Dosage and administration details:

Gefapixant at 50 mg BID for 4 days

Arm title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the

morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Gefapixant at 300 mg BID for 4 days

Number of subjects in period 3	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Started	3	4	3
Completed	3	4	3
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 3	Gefapixant 300 mg>Placebo>Gefapixant 50 mg	Placebo> Gefapixant 50 mg>Gefapixant 300 mg	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Started	3	3	4
Completed	3	3	3
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Period 4

Period 4 title	Wash-out
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Arm description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Arm description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Arm description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Started	3	4	3
Completed	3	3	3
Not completed	0	1	0
Personal reasons	-	1	-

Number of subjects in period 4	Gefapixant 300 mg>Placebo>Gefapixant 50 mg	Placebo> Gefapixant 50 mg>Gefapixant 300 mg	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Started	3	3	3
Completed	3	3	3
Not completed	0	0	0
Personal reasons	-	-	-

Period 5	
Period 5 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Arm description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

Arm title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Arm description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

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

Dosage and administration details:

Gefapixant at 300 mg BID for 4 days

Arm title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details:

Matching placebo to mimic gefapixant 300 mg BID for 4 days

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

Dosage and administration details:

Matching placebo to mimic gefapixant 50 mg BID for 4 days

Arm title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Arm description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

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

Dosage and administration details: Gefapixant at 50 mg BID for 4 days	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo to mimic gefapixant 300 mg BID for 4 days	
Arm title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg
Arm description: Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Arm type	Experimental
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Gefapixant 300 mg BID for 4 days	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo to mimic gefapixant 50 mg BID for 4 days	
Arm title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Arm description: Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching placebo to mimic gefapixant 300 mg BID for 4 days	
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	AF-219 MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Gefapixant 50 mg BID for 4 days	

Number of subjects in period 5	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Started	3	3	3
Completed	3	3	3

Number of subjects in period 5	Gefapixant 300 mg>Placebo>Gefapixant 50 mg	Placebo> Gefapixant 50 mg>Gefapixant 300 mg	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Started	3	3	3
Completed	3	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo
Reporting group description:	
Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg
Reporting group description:	
Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Reporting group description:	
Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg
Reporting group description:	
Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg
Reporting group description:	
Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	
Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Reporting group description:	
Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3	

Reporting group values	Gefapixant 50 mg>Gefapixant 300 mg>Placebo	Gefapixant 50 mg>Placebo>Gefapixant 300 mg	Gefapixant 300 mg>Gefapixant 50 mg>Placebo
Number of subjects	3	4	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	4	3
From 65-84 years	0	0	0

85 years and over	0	0	0

Age Continuous			
Units: years			
arithmetic mean	35.7	27.5	43.3
standard deviation	± 7.0	± 7.6	± 7.6
Sex: Female, Male			
Units:			
Female	1	1	2
Male	2	3	1
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	4	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	4	3
Unknown or Not Reported	0	0	0

Reporting group values	Gefapixant 300 mg>Placebo>Gefapixant 50 mg	Placebo> Gefapixant 50 mg>Gefapixant 300 mg	Placebo> Gefapixant 300 mg>Gefapixant 50 mg
Number of subjects	3	3	4
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	3	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	31.3	52.7	40.0
standard deviation	± 8.0	± 8.1	± 14.3
Sex: Female, Male			
Units:			
Female	0	1	2
Male	3	2	2

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	3	4
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	3	4
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	20		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units:			
Female	7		
Male	13		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	20		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	20		

Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Reporting group description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Reporting group description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Reporting group description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Reporting group description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Reporting group description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Reporting group description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Reporting group description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Reporting group description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Gefapixant 300 mg>Placebo

Reporting group description:

Gefapixant 50 mg twice daily (BID) on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2 followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 50 mg>Placebo>Gefapixant 300 mg

Reporting group description:

Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Gefapixant 50 mg>Placebo

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Gefapixant 300 mg>Placebo>Gefapixant 50 mg

Reporting group description:

Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 50 mg>Gefapixant 300 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Reporting group title	Placebo> Gefapixant 300 mg>Gefapixant 50 mg

Reporting group description:

Placebo BID on Days 1-3 and once daily in the morning Day 4 in Period 1, followed by a washout period of ≥7 days, then Gefapixant 300 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 2, followed by a washout period of ≥7 days, then Gefapixant 50 mg BID on Days 1-3 and once daily in the morning Day 4 in Period 3

Subject analysis set title	Gefapixant 50
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received gefapixant 50 mg twice daily for 3.5 days during one period of the study

Subject analysis set title	Gefapixant 300
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received gefapixant 300 mg twice daily for 3.5 days during one period of the study

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received placebo twice daily for 3.5 days during each period of the study

Subject analysis set title	Screening
Subject analysis set type	Per protocol

Subject analysis set description:

Screening (Day -21 to Day -1)

Primary: Provocative Concentration (PC20) After Methacholine Challenge

End point title	Provocative Concentration (PC20) After Methacholine Challenge

End point description:

The provocative concentration (PC) of inhaled methacholine required to reduce forced expiratory volume in 1 second (FEV1) by 20% (PC20) was calculated from the methacholine challenge at screening and 2 hours (+15 minutes) post dose on Day 3 of each Treatment Period using a five-breath dosimeter method. The primary endpoint was the methacholine PC20 value normalized by means of a log (base 2) transformation, at 2 dose levels compared with placebo in participants with asthma following provocation with methacholine.
Analysis population included all randomized participants who received at least 1 dose of study medication and had any postdose efficacy evaluations for a given Treatment Period and who completed all 3 Treatment Periods.

End point type	Primary

End point timeframe:

Screening (Day -21 to Day -1) and Day 3

End point values	Gefapixant 50	Gefapixant 300	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	18	18	
Units: log [mg/mL]				
geometric mean (geometric coefficient of variation)	0.91 (± 214.4)	0.84 (± 181.0)	0.82 (± 260.1)	

Statistical analyses

Statistical analysis title	Gefapixant 50 mg vs. Placebo

Statistical analysis description:

Analysis was based on an ANOVA model with log (base 2) PC20 methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.

Comparison groups	Gefapixant 50 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616
Method	ANOVA
Parameter estimate	Geometric means ratio
Point estimate	1.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.734
upper limit	1.673

Statistical analysis title	Gefapixant 50 mg vs. Gefapixant 300 mg

Statistical analysis description:

Analysis was based on an ANOVA model with log (base 2) PC20 methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.

Comparison groups	Gefapixant 50 v Gefapixant 300
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.671
Method	ANOVA
Parameter estimate	Geometric means ratio
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.607
upper limit	1.384

Statistical analysis title	Gefapixant 300 mg vs. Placebo

Statistical analysis description:

Analysis was based on an ANOVA model with log (base 2) PC20 methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.

Comparison groups	Gefapixant 300 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	ANOVA
Parameter estimate	Geometric means ratio
Point estimate	1.016

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.673
upper limit	1.534

Secondary: Highest FEV1 After Methacholine Challenge

End point title	Highest FEV1 After Methacholine Challenge

End point description:

Serial FEV1 was measured post inhalation of methacholine challenges for 90 minutes. The highest FEV1 at 5, 15, 30, 45, 60, and 90 minutes following methacholine challenge were evaluated for each subject. The minimum highest FEV1 was derived using the first three available measures that cover the first 30 minutes after the challenge.
Analysis population included all randomized participants who received at least 1 dose of study medication and had any postdose efficacy evaluations for a given Treatment Period and who completed all 3 Treatment Periods.

End point type	Secondary

End point timeframe:

Screening (Day -21 to Day -1) and Day 3

End point values	Gefapixant 50	Gefapixant 300	Placebo	Screening
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	18	18	18
Units: Liters				
arithmetic mean (standard deviation)				
+ 5 minutes	2.53 (± 0.70)	2.43 (± 0.71)	2.54 (± 0.75)	2.44 (± 0.66)
+15 minutes	2.72 (± 0.80)	2.67 (± 0.83)	2.77 (± 0.84)	2.69 (± 0.75)
+30 minutes	2.93 (± 0.88)	2.83 (± 0.86)	2.94 (± 0.89)	2.86 (± 0.82)
+45 minutes	3.02 (± 0.88)	2.99 (± 0.90)	3.03 (± 0.93)	2.93 (± 0.83)
+60 minutes	3.11 (± 0.93)	3.06 (± 0.91)	3.14 (± 0.96)	2.99 (± 0.84)
+90 minutes	3.15 (± 0.93)	3.12 (± 0.90)	3.18 (± 0.95)	3.10 (± 0.88)
Minimum Highest FEV1	2.53 (± 0.70)	2.43 (± 0.71)	2.54 (± 0.75)	2.44 (± 0.66)

Statistical analyses

Statistical analysis title	Gefapixant 300 mg vs Placebo

Statistical analysis description:

Analysis is based on an ANOVA model with minimum highest FEV1 after methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.

Comparison groups	Gefapixant 300 v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.008

Statistical analysis title	Gefapixant 50 mg vs. Gefapixant 300 mg
Statistical analysis description:	
Analysis is based on an ANOVA model with minimum highest FEV1 after methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.	
Comparison groups	Gefapixant 50 v Gefapixant 300
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.218
upper limit	0.02

Statistical analysis title	Gefapixant 50 mg vs. Placebo
Statistical analysis description:	
Analysis is based on an ANOVA model with minimum highest FEV1 after methacholine challenge at each period as dependent variable, treatment and period as fixed effects and participant as random effect.	
Comparison groups	Gefapixant 50 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.843
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.107

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 42 days	
Adverse event reporting additional description:	
All-cause mortality events were assessed for all randomized participants. Non-serious and Serious AEs were assessed for all participants who were randomized and received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Gefapixant 50 mg
Reporting group description:	
Participants received gefapixant 50 mg twice daily for 3.5 days during one period of the study	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo twice daily for 3.5 days during each period of the study	
Reporting group title	Gefapixant 300 mg
Reporting group description:	
Participants received gefapixant 300 mg twice daily for 3.5 days during one period of the study	

Serious adverse events	Gefapixant 50 mg	Placebo	Gefapixant 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Gefapixant 50 mg	Placebo	Gefapixant 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)	8 / 20 (40.00%)	19 / 19 (100.00%)
Injury, poisoning and procedural complications			
Soft tissue injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	8 / 19 (42.11%)	6 / 20 (30.00%)	6 / 19 (31.58%)
occurrences (all)	9	6	6
Dysgeusia			
subjects affected / exposed	13 / 19 (68.42%)	0 / 20 (0.00%)	18 / 19 (94.74%)
occurrences (all)	13	0	18
Hypogeusia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Irritable bowel syndrome			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	3 / 19 (15.79%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Macule			

subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2013	Amendment 1: The main significant changes were to the Borg CR 10 Scale® for use in providing a measure of participants' perception of dyspnea, changes in procedures for breaking the blind and screening measures.
14 March 2014	Amendment 2: The main significant changes were that the population used for analysis was changed from the intent-to-treat population to the per protocol population as well as changes to the procedures for protocol deviations and the analysis plans.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported