Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN027)

Summary

EudraCT number	2017-000537-31
Trial protocol	CZ ES FR DK GB PL HU
Global end of trial date	17 August 2020

Results information

Result version number	v1 (current)
This version publication date	28 July 2021
First version publication date	28 July 2021

Trial information

Trial identification

Sponsor protocol code	7264-027

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03449134
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	21 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2020
Global end of trial reached?	Yes
Global end of trial date	17 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study will be to evaluate the efficacy of gefapixant in reducing cough frequency as measured over a 24-hour period at Week 12, and to evaluate the safety and tolerability of gefapixant. The primary hypothesis is that at least one gefapixant dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 12.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 49
Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	Czechia: 53
Country: Number of subjects enrolled	Denmark: 42
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	Peru: 46
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	United States: 123

Worldwide total number of subjects	732
EEA total number of subjects	227

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)	447
From 65 to 84 years	283
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 732 participants randomized to the 52-week treatment period, 730 participants received at least 1 dose of study intervention. After the main study, 41 participants continued in an optional Off-Treatment (Off-Tx) Durability observational study period (no treatment).

Period 1

Period 1 title	52-Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.

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

Dosage and administration details:

Participants receive dose-matched placebo tablets orally BID during the 12-week main study period and during the 40-week extension period.

Arm title	Gefapixant 15 mg BID

Arm description:

Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.

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:

Participants receive placebo to gefapixant 45 mg tablet orally BID during the 12-week main study period and during the 40-week extension period.

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

Dosage and administration details:

Gefapixant 15 mg tablet administered orally BID during the 12-week main study period and during the 40-week extension period.

Arm title	Gefapixant 45 mg BID

Arm description:

Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period.

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

Dosage and administration details:

Gefapixant 45 mg tablet administered orally BID during the 12-week main study period and during the 40-week extension period.

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

Dosage and administration details:

Participants receive placebo to gefapixant 15 mg tablet orally BID during the 12-week main study period and during the 40-week extension period.

Number of subjects in period 1	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID
Started	244	244	244
Treated	243	244	243
Completed	199	200	184
Not completed	45	44	60
Adverse event, serious fatal	2	1	-
Site Closure	1	-	-
Physician decision	2	3	3
Consent withdrawn by subject	37	39	55
Screen Failure	1	-	1
Lost to follow-up	2	1	1

Period 2

Period 2 title	12-Week Off-Treatment Durability Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo: Off Tx

Arm description:

Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 15 mg BID: Off Tx

Arm description:

Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Gefapixant 45 mg BID: Off Tx

Arm description:

Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Placebo: Off Tx	Gefapixant 15 mg BID: Off Tx	Gefapixant 45 mg BID: Off Tx
Started	10	18	13
Completed	10	18	13

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants continued in the optional Off-Treatment Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.	
Reporting group title	Gefapixant 15 mg BID
Reporting group description:	
Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.	
Reporting group title	Gefapixant 45 mg BID
Reporting group description:	
Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period.	

Reporting group values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID
Number of subjects	244	244	244
Age categorical Units: Participants			
Adults (18-64 years)	147	152	148
From 65-84 years	97	91	95
85 years and over	0	1	1
Age Continuous Units: Years			
arithmetic mean	57.9	59.6	59.5
standard deviation	± 13.1	± 11.7	± 13.1
Sex: Female, Male Units: Participants			
Female	182	181	181
Male	62	63	63
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	7	6	8
Asian	35	35	34
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	3	4
White	190	195	187
More than one race	8	5	11
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	33	35	33
Not Hispanic or Latino	204	205	208
Unknown or Not Reported	7	4	3
Geographic Region			
Geographic region of enrollment with 5 categories: Asia-Pacific, Europe, North America, Others, and Missing.			
Units: Subjects			

Asia Pacific	35	34	34
Europe	121	123	122
North America	56	55	56
Others	31	32	32
Missing	1	0	0
Baseline 24-hour Coughs per Hour			
24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours (denominator could be different if the recording period was actually <24 hours but ≥20 hours). Baseline assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. All participants with 24-hour Coughs per Hour data available at baseline were analyzed (n=232, 235, 237).			
Units: coughs/hour			
arithmetic mean	38.07	26.79	28.53
standard deviation	± 79.42	± 21.13	± 37.14

Reporting group values	Total		
Number of subjects	732		
Age categorical Units: Participants			
Adults (18-64 years)	447		
From 65-84 years	283		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	544		
Male	188		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	21		
Asian	104		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	11		
White	572		
More than one race	24		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	101		
Not Hispanic or Latino	617		
Unknown or Not Reported	14		
Geographic Region			
Geographic region of enrollment with 5 categories: Asia-Pacific, Europe, North America, Others, and Missing.			
Units: Subjects			
Asia Pacific	103		
Europe	366		
North America	167		

Others	95		
Missing	1		

Baseline 24-hour Coughs per Hour			
24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours (denominator could be different if the recording period was actually <24 hours but ≥20 hours). Baseline assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. All participants with 24-hour Coughs per Hour data available at baseline were analyzed (n=232, 235, 237).			
Units: coughs/hour			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.	
Reporting group title	Gefapixant 15 mg BID
Reporting group description:	
Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.	
Reporting group title	Gefapixant 45 mg BID
Reporting group description:	
Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period.	
Reporting group title	Placebo: Off Tx
Reporting group description:	
Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).	
Reporting group title	Gefapixant 15 mg BID: Off Tx
Reporting group description:	
Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).	
Reporting group title	Gefapixant 45 mg BID: Off Tx
Reporting group description:	
Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).	

Primary: Model-Based Geometric Mean Ratio (GMR) of 24-hour Objective Coughs Per Hour (Week 12/Baseline)

End point title	Model-Based Geometric Mean Ratio (GMR) of 24-hour Objective Coughs Per Hour (Week 12/Baseline)
End point description:	
24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours. Assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. A longitudinal analysis of covariance (ANCOVA) model was applied to log-transformed cough counts to determine geometric mean (GM) 24-hour objective coughs per hour at baseline and Week 12 on the original scale. The GMR corresponding to the Week 12 GM 24-hour objective coughs per hour divided by the Baseline GM 24-hour objective coughs per hour was reported for all treatment study arms. All randomized participants in the analysis model who had taken at least 1 dose of study intervention and provided at least 1 baseline and at least 1 Week 12 24-hour cough observation during the treatment period were analyzed.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	227	217	
Units: ratio				
geometric mean (confidence interval 95%)	0.47 (0.41 to 0.54)	0.48 (0.41 to 0.55)	0.38 (0.33 to 0.44)	

Statistical analyses

Statistical analysis title	24-Hour Coughs/Hour ERR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (PBO) (i.e. estimated percent change difference) was calculated by 100 (e**DIFF -1), where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

Comparison groups	Placebo v Gefapixant 45 mg BID
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.041 [1]
Method	ANCOVA
Parameter estimate	Estimated Percent Change Difference
Point estimate	-18.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.92
upper limit	-0.86

Notes:

[1] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Statistical analysis title	24-Hour Coughs/Hour ERR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by 100 (e**DIFF -1), where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.874 [2]
Method	ANCOVA
Parameter estimate	Estimated Percent Change Difference
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.13
upper limit	22.99

Notes:

[2] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Primary: Number of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up

End point title	Number of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up[3]

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants with at least one AE during either the 52-week treatment period or 2-week telephone follow-up was reported for all treatment study arms.

All randomized participants who received at least 1 dose of study intervention during the 52-week treatment period were analyzed. Per protocol, participants who continued in the optional Off-Treatment observational period were not included in the primary safety analysis.

End point type	Primary

End point timeframe:

Up to approximately 54 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	244	243	
Units: Participants	184	186	208	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Treatment Due to AEs

End point title	Number of Participants Who Discontinued Treatment Due to AEs[4]

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants with at least one AE during either the 52-week treatment period or 2-week telephone follow-up was reported for all treatment study arms.

All randomized participants who received at least 1 dose of study intervention during the 52-week treatment period were analyzed. Per protocol, participants who continued in the optional Off-Treatment observational period were not included in the primary safety analysis.

End point type	Primary

End point timeframe:

Up to approximately 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	244	243	
Units: Participants	14	15	51	

Statistical analyses

No statistical analyses for this end point

Secondary: Model-Based Geometric Mean Ratio (GMR) of Awake Objective Coughs Per Hour (Week 12/Baseline)

End point title	Model-Based Geometric Mean Ratio (GMR) of Awake Objective Coughs Per Hour (Week 12/Baseline)

End point description:

Awake objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) while the participant is awake divided by the total duration (in hours) for the monitoring period that the participant was awake. Assessment was based on 24-hour sound recordings using a digital recording device. A longitudinal ANCOVA model was applied to log-transformed cough counts to determine GM awake objective coughs per hour at baseline and Week 12 on the original scale. The GMR corresponding to the Week 12 GM awake objective coughs per hour divided by the Baseline GM awake objective coughs per hour was reported for all treatment study arms.

All randomized participants in the analysis model who had taken at least 1 dose of study intervention and provided at least 1 baseline and at least 1 Week 12 awake cough observation during the treatment period were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	227	217	
Units: ratio				
geometric mean (confidence interval 95%)	0.46 (0.40 to 0.53)	0.47 (0.41 to 0.55)	0.38 (0.33 to 0.44)	

Statistical analyses

Statistical analysis title	Awake Coughs/Hour ERR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by 100 (e**DIFF -1), where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

Comparison groups	Placebo v Gefapixant 45 mg BID

Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.056 [5]
Method	ANCOVA
Parameter estimate	Estimated Percent Change Difference
Point estimate	-17.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.57
upper limit	0.5

Notes:

[5] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Statistical analysis title	Awake Coughs/Hour ERR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by 100 (e**DIFF -1), where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.77 [6]
Method	ANCOVA
Parameter estimate	Estimated Percent Change Difference
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.33
upper limit	25.19

Notes:

[6] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Secondary: Percentage of Participants (Model-Based) With a ≤ -30% Change from Baseline in 24-hour Objective Coughs Per Hour at Week 12

End point title	Percentage of Participants (Model-Based) With a ≤ -30% Change from Baseline in 24-hour Objective Coughs Per Hour at Week 12

End point description:

24-hour coughs/hour defined as the total number of cough events during the 24-hour monitoring period divided by 24 hours. Assessment based on 24-hour sound recordings using a digital recording device. Percent change in 24-hour coughs/hour = (change from baseline in 24-hour coughs per hour/baseline 24-hour coughs per hour) ×100%. Negative values indicate a decrease in cough rate, while positive values indicate an increase in cough rate. A participant considered a responder if percent change from baseline in 24-hour coughs/hour was ≤ -30% (or a ≥30% reduction from baseline); and considered a non-responder otherwise. Percentage of participants (logistic regression model-based) with a ≤ -30% change from baseline in 24-hour coughs/hour at Week 12 reported for all treatment study arms.

All randomized participants in the analysis model who had taken ≥1 dose of study intervention and had available 24-hour cough data at baseline and ≥1 available post-baseline measurement were analyzed.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	227	217	
Units: Percentage of Participants				
number (not applicable)	65.9	66.2	69.9	

Statistical analyses

Statistical analysis title	24-Hour Coughs/Hour OR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 45 mg BID
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.416
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.86

Statistical analysis title	24-Hour Coughs/Hour OR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.55

Secondary: Percentage of Participants (Model-Based) With a ≤ -1.3-point Change from Baseline in Mean Weekly Cough Severity Diary (CSD) Total Score at Week 12

End point title	Percentage of Participants (Model-Based) With a ≤ -1.3-point Change from Baseline in Mean Weekly Cough Severity Diary (CSD) Total Score at Week 12

End point description:

The CSD evaluates the frequency of cough, intensity of cough and disruption and has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score was the sum of these seven item scores (Min=0, Max=70). Mean weekly total score was defined as the average of mean total daily scores collected during the week prior to each visit. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Day -6 to Day 0). Participants were considered responders if the change from baseline in mean weekly CSD total score was ≤ -1.3 points (or a ≥1.3 point reduction from baseline); and considered non-responder otherwise. The percentage of participants with a ≤ -1.3 point change from baseline in CSD at Week 12 was reported for all treatment study arms.

All randomized participants who received ≥1 dose of study intervention, had available CSD data at baseline and ≥1 available post-baseline measurement were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	237	241	234	
Units: Percentage of Participants				
number (not applicable)	52.4	62.1	60.5	

Statistical analyses

Statistical analysis title	CSD OR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 45 mg BID

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.05

Statistical analysis title	CSD OR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.18

Secondary: Percentage of Participants (Model-Based) With a ≤ -2.7-point Change from Baseline in Mean Weekly CSD Total Score at Week 12

End point title	Percentage of Participants (Model-Based) With a ≤ -2.7-point Change from Baseline in Mean Weekly CSD Total Score at Week 12

End point description:

The CSD evaluates frequency of cough, intensity of cough and disruption and has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score was the sum of these seven item scores (Min=0, Max=70). Mean weekly total score was defined as the average of the mean total daily scores collected during the week prior to each visit. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Day -6 to Day 0). Participants were considered responders if the change from baseline in mean weekly CSD total score was ≤ -2.7 points (or a ≥2.7 point reduction from baseline); and considered non-responder otherwise. The percentage of participants with a ≤ -2.7 point change from baseline in CSD at Week 12 was reported for all treatment study arms.

All randomized participants who had taken ≥1 dose of study intervention and had available CSD data at baseline and ≥1 available post-baseline measurement were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	237	241	234	
Units: Percentage of Participants				
number (not applicable)	28.6	37.9	40.1	

Statistical analyses

Statistical analysis title	CSD OR: PBO vs Gefapixant 45 mg
Statistical analysis description:	
Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.	
Comparison groups	Placebo v Gefapixant 45 mg BID
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	2.54

Statistical analysis title	CSD OR: PBO vs Gefapixant 15 mg
Statistical analysis description:	
Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.	
Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.3

Secondary: Percentage of Participants (Model-Based) With a ≤ -30 millimeter (mm) Change from Baseline in Cough Severity Visual Analog Scale (VAS) Score at Week 12

End point title	Percentage of Participants (Model-Based) With a ≤ -30 millimeter (mm) Change from Baseline in Cough Severity Visual Analog Scale (VAS) Score at Week 12

End point description:

Cough severity was scored using the Cough Severity VAS, a single-item question asking the participant to rate the severity of their cough "today" using a 100 mm VAS (100-point scale) ranging from 0 ("No Cough") to 100 ("Extremely Severe Cough"). Mean weekly VAS score was derived as the average of VAS scores collected during the week prior to each visit. Baseline was defined as the average VAS scores collected during the week prior to Day 1 (Day -6 to Day 0). A participant was considered a responder if the change from baseline in mean weekly Cough Severity VAS score was ≤-30 mm (or a ≥30 mm reduction from baseline); and considered non-responder otherwise. The percentage of participants with ≤ -30 mm change from baseline in Cough Severity VAS at Week 12 was reported for all treatment study arms.

All randomized participants who had taken ≥1 dose of study intervention and had available Cough Severity VAS data at baseline and ≥1 available post-baseline measurement were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	237	241	234	
Units: Percentage of Participants				
number (not applicable)	31.3	36.7	41.2	

Statistical analyses

Statistical analysis title	Cough Severity VAS OR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline VAS score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 45 mg BID
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.3

Statistical analysis title	Cough Severity VAS OR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline VAS score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.89

Secondary: Percentage of Participants (Model-Based) With a ≥1.3-point Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score at Week 12

End point title	Percentage of Participants (Model-Based) With a ≥1.3-point Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score at Week 12

End point description:

The LCQ assesses the impact of chronic cough on health-related quality of life. It consists of 19 items which are divided over 3 domains: Physical, Psychological, and Social. A 7-point Likert scale is used to rate each item. For each domain, the domain score (range 1-7) is the sum of individual item score within the domain divided by the number of items in the domain. LCQ total score is the sum of the three domain scores and ranges from 3-21; with a higher score corresponding to a better health status. A participant was considered a responder if the change from baseline in LCQ total score was ≥1.3-points (increase from baseline); and considered non-responder otherwise. The percentage of participants with a ≥1.3-point change from baseline in LCQ total score at Week 12 was reported for all treatment study arms.

All randomized participants who had taken ≥1 dose of study intervention and had available LCQ data at baseline and ≥1 available post-baseline measurement were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Gefapixant 15 mg BID	Gefapixant 45 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	217	226	214	
Units: Percentage of Participants				
number (not applicable)	61.3	68.8	67.3	

Statistical analyses

Statistical analysis title	LCQ OR: PBO vs Gefapixant 45 mg

Statistical analysis description:

Comparison based on a logistic regression model that included visit, treatment-by-visit interaction, gender, region, baseline LCQ score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 45 mg BID
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.98

Statistical analysis title	LCQ OR: PBO vs Gefapixant 15 mg

Statistical analysis description:

Comparison based on a logistic regression model that included visit, treatment-by-visit interaction, gender, region, baseline LCQ score, and the interaction of baseline (underlying continuous response) by visit as covariates.

Comparison groups	Placebo v Gefapixant 15 mg BID
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-Treatment Period (plus 2-week telephone follow-up): Up to Week 54; Off-Treatment (Off-Tx) Period: From Week 52 through Week 64 (approximately 12 weeks)

Adverse event reporting additional description:

All-Cause Mortality (ACM) reported for all randomized participants. Serious and Nonserious AEs reported for participants treated during 52-Week Treatment Period. AEs reported separately for treatment period and optional Off-Tx Period. Per protocol, only ACM, drug-related serious and nonserious AEs, and pregnancies monitored during Off-Tx Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0, 23.1

Reporting groups

Reporting group title	Placebo: On Tx

Reporting group description:

Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.

Reporting group title	Gefapixant 15 mg BID: On Tx

Reporting group description:

Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.

Reporting group title	Gefapixant 45 mg BID: On Tx

Reporting group description:

Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period.

Reporting group title	Placebo: Off Tx

Reporting group description:

Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Reporting group title	Gefapixant 15 mg BID: Off Tx

Reporting group description:

Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Reporting group title	Gefapixant 45 mg BID: Off Tx

Reporting group description:

Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

Serious adverse events	Placebo: On Tx	Gefapixant 15 mg BID: On Tx	Gefapixant 45 mg BID: On Tx
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 243 (5.76%)	17 / 244 (6.97%)	13 / 243 (5.35%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin abrasion			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac amyloidosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall cyst			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			

subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Bursitis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma viral infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			

subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 243 (0.00%)	1 / 244 (0.41%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 244 (0.00%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 244 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo: Off Tx	Gefapixant 15 mg BID: Off Tx	Gefapixant 45 mg BID: Off Tx
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Accidental death			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin abrasion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac amyloidosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall cyst			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo: On Tx	Gefapixant 15 mg BID: On Tx	Gefapixant 45 mg BID: On Tx
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 243 (53.09%)	140 / 244 (57.38%)	179 / 243 (73.66%)
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 243 (0.00%)	3 / 244 (1.23%)	33 / 243 (13.58%)
occurrences (all)	0	5	37
Dysgeusia			
subjects affected / exposed	8 / 243 (3.29%)	22 / 244 (9.02%)	88 / 243 (36.21%)
occurrences (all)	9	25	101
Headache			
subjects affected / exposed	31 / 243 (12.76%)	34 / 244 (13.93%)	29 / 243 (11.93%)
occurrences (all)	55	57	51
Hypogeusia			
subjects affected / exposed	1 / 243 (0.41%)	5 / 244 (2.05%)	13 / 243 (5.35%)
occurrences (all)	1	5	14
Taste disorder			
subjects affected / exposed	2 / 243 (0.82%)	2 / 244 (0.82%)	24 / 243 (9.88%)
occurrences (all)	2	2	24
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	14 / 243 (5.76%)	15 / 244 (6.15%)	12 / 243 (4.94%)
occurrences (all)	19	19	23
Dry mouth			
subjects affected / exposed	6 / 243 (2.47%)	7 / 244 (2.87%)	13 / 243 (5.35%)
occurrences (all)	7	7	13
Nausea			
subjects affected / exposed	13 / 243 (5.35%)	8 / 244 (3.28%)	17 / 243 (7.00%)
occurrences (all)	22	8	20
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	16 / 243 (6.58%)	9 / 244 (3.69%)	11 / 243 (4.53%)
occurrences (all)	21	10	18
Cough			
subjects affected / exposed	10 / 243 (4.12%)	14 / 244 (5.74%)	16 / 243 (6.58%)
occurrences (all)	11	14	17
Oropharyngeal pain			
subjects affected / exposed	10 / 243 (4.12%)	13 / 244 (5.33%)	14 / 243 (5.76%)
occurrences (all)	14	18	14
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 243 (3.29%)	13 / 244 (5.33%)	9 / 243 (3.70%)
occurrences (all)	8	18	12
Back pain			
subjects affected / exposed	19 / 243 (7.82%)	14 / 244 (5.74%)	20 / 243 (8.23%)
occurrences (all)	21	17	27
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 243 (4.53%)	20 / 244 (8.20%)	11 / 243 (4.53%)
occurrences (all)	12	25	17
Localised infection			
subjects affected / exposed	1 / 243 (0.41%)	1 / 244 (0.41%)	1 / 243 (0.41%)
occurrences (all)	1	1	1
Nasopharyngitis			
subjects affected / exposed	51 / 243 (20.99%)	47 / 244 (19.26%)	50 / 243 (20.58%)
occurrences (all)	75	60	63

Respiratory tract infection			
subjects affected / exposed	1 / 243 (0.41%)	2 / 244 (0.82%)	0 / 243 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	9 / 243 (3.70%)	18 / 244 (7.38%)	13 / 243 (5.35%)
occurrences (all)	12	20	19
Urinary tract infection			
subjects affected / exposed	11 / 243 (4.53%)	14 / 244 (5.74%)	9 / 243 (3.70%)
occurrences (all)	14	14	13

Non-serious adverse events	Placebo: Off Tx	Gefapixant 15 mg BID: Off Tx	Gefapixant 45 mg BID: Off Tx
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	1 / 13 (7.69%)
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypogeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 18 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 18 (0.00%) 0	0 / 13 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2017	Major changes of Amendment (AM) 1 include revision of eligibility criteria and editorial clarifications.
27 September 2018	Major changes of Amendment AM 2 include a clarification of treatment of co-morbid conditions, and an update of the estimated glomerular filtration rate (eGFR).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported