Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis - The ASPEN Study

Summary

EudraCT number	2020-003688-25
Trial protocol	DE PT DK NL IE HU GR PL BG LT SK AT FR EE BE IT ES
Global end of trial date	28 October 2024

Results information

Result version number	v1 (current)
This version publication date	11 May 2025
First version publication date	11 May 2025

Trial information

Trial identification

Sponsor protocol code	INS1007-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04594369
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT Number: jRCT2031210048

Notes:

Sponsors

Sponsor organisation name	Insmed Incorporated
Sponsor organisation address	700 US Highway 202/206, Bridgewater, United States, 08807-1704
Public contact	Insmed Medical Information, Insmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.com
Scientific contact	Insmed Medical Information, Insmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002905-PIP01-20
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 October 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of brensocatib at 10 milligram (mg) and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs) over the 52-week treatment period.

Protection of trial subjects:

This trial was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, the International Council for Harmonisation (ICH) Guidelines, and is consistent with the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 90
Country: Number of subjects enrolled	Argentina: 258
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Bulgaria: 85
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 78
Country: Number of subjects enrolled	Colombia: 19
Country: Number of subjects enrolled	Denmark: 48
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 75
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 84
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Japan: 87
Country: Number of subjects enrolled	Korea, Republic of: 45

Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Mexico: 47
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	New Zealand: 46
Country: Number of subjects enrolled	Peru: 41
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Türkiye: 36
Country: Number of subjects enrolled	United Kingdom: 46
Country: Number of subjects enrolled	United States: 241
Worldwide total number of subjects	1721
EEA total number of subjects	490

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)	41
Adults (18-64 years)	841
From 65 to 84 years	832
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 373 sites in 36 countries from 01 Dec 2020 to 28 Oct 2024.

Pre-assignment

Screening details:

A total of 2296 participants were screened, 1767 participants with non-cystic fibrosis bronchiectasis were enrolled in the study. Due to the war in Ukraine, 44 participants from Ukraine were not analysed, 2 additional participants were not analysed due to serios GCP non-compliance.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Brensocatib 10 mg

Arm description:

Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Brensocatib
Investigational medicinal product code	
Other name	INS1007
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 10 mg tablets, once daily, for 52 weeks.

Arm title	Brensocatib 25 mg

Arm description:

Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Brensocatib
Investigational medicinal product code	
Other name	INS1007
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 25 mg tablets, once daily, for 52 weeks.

Arm title	Placebo

Arm description:

Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received brensocatib matching placebo tablets, once daily, for 52 weeks.

Number of subjects in period 1	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
Started	583	575	563
Completed	458	466	457
Not completed	125	109	106
Adverse event, serious fatal	2	4	8
Other than specified above	60	56	43
Physician decision	2	2	3
Consent withdrawn by subject	40	32	37
Adverse event, non-fatal	10	10	9
Lost to follow-up	10	2	4
Protocol deviation	1	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Brensocatib 10 mg
Reporting group description:	
Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.	
Reporting group title	Brensocatib 25 mg
Reporting group description:	
Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.	

Reporting group values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
Number of subjects	583	575	563
Age Categorical Units: Subjects			
Age continuous Units: Years			
arithmetic mean	59.8	60.6	60.0
standard deviation	± 15.92	± 15.78	± 15.44
Gender categorical Units: Subjects			
Female	385	360	362
Male	198	215	201
Ethnicity Units: Subjects			
Not Hispanic or Latino	391	397	373
Hispanic or Latino	177	164	170
Not Reported	13	13	17
Unknown	2	1	3
Race Units: Subjects			
American Indian or Alaska Native	8	6	9
Asian	63	64	64
Black or African American	2	5	3
Native Hawaiian or Other Pacific Islander	1	0	1
White	431	430	405
Other	15	13	11
Unknown	18	13	14
Not Reported	30	33	45
Multiple	15	11	11

Reporting group values	Total		
Number of subjects	1721		

Age Categorical Units: Subjects			

Age continuous Units: Years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	1107		
Male	614		
Ethnicity Units: Subjects			
Not Hispanic or Latino	1161		
Hispanic or Latino	511		
Not Reported	43		
Unknown	6		
Race Units: Subjects			
American Indian or Alaska Native	23		
Asian	191		
Black or African American	10		
Native Hawaiian or Other Pacific Islander	2		
White	1266		
Other	39		
Unknown	45		
Not Reported	108		
Multiple	37		

End points

End points reporting groups

Reporting group title	Brensocatib 10 mg
Reporting group description:	
Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.	
Reporting group title	Brensocatib 25 mg
Reporting group description:	
Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.	

Primary: Annualized Rate of Pulmonary Exacerbations (PEs)

End point title	Annualized Rate of Pulmonary Exacerbations (PEs)
End point description:	
Pulmonary exacerbation was defined as having 3 or more of these symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. A severe pulmonary exacerbation was that required IV antibacterial drug treatment and/or hospitalization. A minimum of 14 days must have occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 14 days from the prior exacerbation was not considered a new exacerbation. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition. The rate of PE was analysed using the negative binomial model. The Intent-to-Treat (ITT) analysis set included all participants who were randomised.	
End point type	Primary
End point timeframe:	
Up to Week 52	

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	583	575	563	
Units: exacerbation per patient-year				
number (confidence interval 95%)	1.015 (0.910 to 1.132)	1.036 (0.927 to 1.157)	1.286 (1.158 to 1.428)	

Statistical analyses

Statistical analysis title	Brensocatib 25 mg vs Placebo
Statistical analysis description:	
Model treatment & randomization stratification factor=geographic region, sputum sample (Pseudomonas aeruginosa) at start & PE last 12 months, age group (fixed effects) & time at risk (log scale) as offset variable. Robust sandwich covariance estimator used.	
Comparison groups	Brensocatib 25 mg v Placebo

Number of subjects included in analysis	1138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046 [1]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.694
upper limit	0.936

Notes:

[1] - Adjusted p-value = 0.0048. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the primary endpoint was tested at two-sided alpha = 0.01.

Statistical analysis title	Brensocatib 10 mg vs Placebo

Statistical analysis description:

Model treatment & randomization stratification factor=geographic region, sputum sample (Pseudomonas aeruginosa) at start & PE last 12 months, age group (fixed effects) & time at risk (log scale) as offset variable. Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 10 mg v Placebo
Number of subjects included in analysis	1146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 [2]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.789
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.916

Notes:

[2] - Adjusted p-value = 0.0038. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the primary endpoint was tested at two-sided alpha = 0.01.

Secondary: Time to First PE

End point title	Time to First PE

End point description:

PE was defined as 3 or more of these symptoms for at least 48 hours & physician's choice to prescribe antibiotics:1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. Severe PE=IV antibacterial drug treatment and/or hospitalization. Minimum 14 days between one exacerbation onset and next. Any PE in less than 14 days from prior exacerbation was not considered new. Time to first PE=randomisation date to onset date of first exacerbation. Participants with no exacerbation at end of 52-week treatment were censored at Week 52. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition.9999=upper limit of confidence interval was not computable. The ITT analysis set included all participants who were randomised.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	583	575	563	
Units: weeks				
median (confidence interval 95%)	49.000 (40.000 to 9999)	50.714 (37.571 to 9999)	36.714 (31.143 to 41.429)	

Statistical analyses

Statistical analysis title	Brensocatib 25 mg vs placebo

Statistical analysis description:

Estimate of Cox proportional hazard model=effect for treatment, sputum sample for Pseudomonas aeruginosa at screening and PE [<3 or ≥3] in last 12 months, stratification region and age group. Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	1138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0182 [3]
Method	Cox proportional hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.825
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.703
upper limit	0.968

Notes:

[3] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Statistical analysis title	Brensocatib 10 mg vs placebo

Statistical analysis description:

Estimate of Cox proportional hazard model=effect for treatment, sputum sample for Pseudomonas aeruginosa at screening and PE [<3 or ≥3] in last 12 months, stratification region and age group. Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 10 mg v Placebo
Number of subjects included in analysis	1146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [4]
Method	Cox proportional hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.813

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.695
upper limit	0.952

Notes:

[4] - Adjusted p-value = 0.0200. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Secondary: Responder Status for Exacerbation-Free Over the 52-Week Treatment Period

End point title	Responder Status for Exacerbation-Free Over the 52-Week Treatment Period

End point description:

Responder status was based on percentage of participants who were exacerbation free over 52-weeks of treatment period. PE was defined as having 3 or more of these symptoms for at least 48 hours with physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. Minimum of 14 days must have occurred between one PE onset and the next. Any PE in less than 14 days from prior exacerbation was not considered new exacerbation. Independent adjudication committee of pulmonary physicians will adjudicate reported PE events to see if they fulfill protocol definition. For discontinuation prior to Week 52 without having experienced a confirmed PE, responder status imputed by multiple imputation. The ITT analysis set included all participants who were randomised.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	583	575	563	
Units: percentage of participants				
number (not applicable)	48.5	48.5	40.3	

Statistical analyses

Statistical analysis title	Brensocatib 25 mg vs Placebo

Statistical analysis description:

Missing responder status was imputed 100 times. Dataset was analyzed via logistic regression with treatment group, sputum P. aeruginosa status, prior PEs (<3/≥3), region, and age group as fixed effects. Results were then combined using Rubin’s rules.

Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	1138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074 [5]
Method	Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.095
upper limit	1.792

Notes:

[5] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Statistical analysis title	Brensocatib 10 mg vs Placebo

Statistical analysis description:

Missing responder status was imputed 100 times. Dataset was analyzed via logistic regression with treatment group, sputum P. aeruginosa status, prior PEs (<3/≥3), region, and age group as fixed effects. Results were then combined using Rubin’s rules.

Comparison groups	Brensocatib 10 mg v Placebo
Number of subjects included in analysis	1146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059 [6]
Method	Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.105
upper limit	1.806

Notes:

[6] - Adjusted p-value = 0.0200. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Secondary: Change From Baseline at Week 52 in Postbronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change From Baseline at Week 52 in Postbronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point description:

FEV1 was used to assess lung function and is the maximum amount of air that can be exhaled from the lungs in the first second after taking a forced expiration as measured by spirometer. Postbronchodilator FEV1 tests included spirometry tests performed referred to the spirometry performed within 30 minutes after administration of bronchodilator (4 puffs of salbutamol/albuterol, terbutaline or ipratropium). The ITT analysis set included all participants who were randomised. 'Number of subjects analysed' indicates the number of participants with data available for analyses. Baseline was the most recent non-missing assessment determined as best effort prior to the first dose of the investigational product.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	564	551	539	
Units: liter (L)				
least squares mean (standard error)	-0.050 (± 0.0093)	-0.024 (± 0.0099)	-0.062 (± 0.0094)	

Statistical analyses

Statistical analysis title	Brensocatib 25 mg vs placebo

Statistical analysis description:

Analysis on linear repeated measure model=treatment visit, sputum sample for Pseudomonas aeruginosa at start, PE [<3 or ≥3] last 12 months, stratification region, age group (fixed effect) & baseline (covariate). Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	1090
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054 [7]
Method	Linear repeated measures model
Parameter estimate	Difference in LS Mean
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.0136

Notes:

[7] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Statistical analysis title	Brensocatib 10 mg vs placebo

Statistical analysis description:

Analysis on linear repeated measure model=treatment visit, sputum sample for Pseudomonas aeruginosa at start, PE [<3 or ≥3] last 12 months, stratification region, age group (fixed effect) & baseline (covariate). Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 10 mg v Placebo
Number of subjects included in analysis	1103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3841 [8]
Method	Linear repeated measures model
Parameter estimate	Difference in LS Mean
Point estimate	0.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.037
Variability estimate	Standard error of the mean
Dispersion value	0.0132

Notes:

[8] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Secondary: Annualized Rate of Severe PEs

End point title	Annualized Rate of Severe PEs

End point description:

Pulmonary exacerbation was defined as having 3 or more of these symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. A severe PE was defined as those requiring IV antibacterial drug treatment and/or hospitalization. A minimum of 14 days must have occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 14 days from the prior exacerbation was not considered a new exacerbation. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition. The rate of PE will be analysed using the negative binomial model. The ITT analysis set included all participants who were randomised.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	583	575	563	
Units: exacerbation per patient-year				
number (confidence interval 95%)	0.137 (0.103 to 0.182)	0.137 (0.105 to 0.179)	0.185 (0.142 to 0.242)	

Statistical analyses

Statistical analysis title	Brensocatib 10 mg vs placebo

Statistical analysis description:

Analysis based on a negative binomial model including treatment, sputum sample for Pseudomonas aeruginosa at screening, PE [<3 or ≥3] in previous 12 months, stratification region and age group. Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 10 mg v Placebo

Number of subjects included in analysis	1146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1277 [9]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.742
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.505
upper limit	1.089

Notes:

[9] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Statistical analysis title	Brensocatib 25 mg vs placebo

Statistical analysis description:

Analysis based on a negative binomial model including treatment, sputum sample for Pseudomonas aeruginosa at screening, PE [<3 or ≥3] in previous 12 months, stratification region and age group. Robust sandwich covariance estimator used.

Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	1138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1025 [10]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.515
upper limit	1.062

Notes:

[10] - Adjusted p-value = 0.2050. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Secondary: Change from Baseline at Week 52 in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants

End point title	Change from Baseline at Week 52 in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants

End point description:

QOL-B is validated, self-administered patient-reported outcome (PRO) assessing symptoms, functioning, and health-related quality of life in participants with non-cystic fibrosis bronchiectasis (NCFBE). It includes 37 items across 8 domains: Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, and Treatment Burden. Each item is scored from 1 to 4, with domain scores standardized on 0-100 scale, where higher scores represent fewer symptoms or better functioning. Positive change from Baseline indicates improvement in symptoms. For this outcome, change in respiratory symptoms domain score from Baseline is reported. Baseline refers to most recent assessment on or before study day 1. ITT analysis set included all randomised adult participants, with 'Number of subjects analysed' is number of adult participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	487	495	486	
Units: score on scale				
least squares mean (standard error)	6.841 (± 0.7706)	8.575 (± 0.7556)	4.809 (± 0.7500)	

Statistical analyses

Statistical analysis title	Brensocatib 25 mg vs placebo

Statistical analysis description:

Analysis based on a linear repeated measures model with treatment group, visit, sputum sample for Pseudomonas aeruginosa at screening, pulmonary exacerbations [<3 or ≥3] in previous 12 months, stratification region fixed effect, baseline as covariate.

Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [11]
Method	linear repeated measures model
Parameter estimate	LS mean difference
Point estimate	3.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	5.852
Variability estimate	Standard error of the mean
Dispersion value	1.0642

Notes:

[11] - Adjusted p-value = 0.2050. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Statistical analysis title	Brensocatib 10 mg vs placebo

Statistical analysis description:

Analysis based on a linear repeated measures model with treatment group, visit, sputum sample for Pseudomonas aeruginosa at screening, pulmonary exacerbations [<3 or ≥3] in previous 12 months, stratification region fixed effect, baseline as covariate.

Comparison groups	Brensocatib 10 mg v Placebo

Number of subjects included in analysis	973
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0594 [12]
Method	linear repeated measures model
Parameter estimate	LS mean difference
Point estimate	2.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	4.143
Variability estimate	Standard error of the mean
Dispersion value	1.0775

Notes:

[12] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

Secondary: Number of Participants who Experienced at Least one Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants who Experienced at Least one Treatment-Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are AEs that occurred on or after the date of first dose of study drugs and within 28 days after the end of treatment. The safety analysis set included all participants who were randomised and received at least 1 dose of brensocatib or placebo.

End point type	Secondary

End point timeframe:

Up to Week 56

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	582	574	563	
Units: participants	452	440	448	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Brensocatib in Adults (Main Study)

End point title	Plasma Concentration of Brensocatib in Adults (Main Study)[13]

End point description:

Pharmacokinetics (PK) Concentration Analysis Set included adult participants who consented to

participate in the main study in adult's cohort, received at least 1 dose of brensocatib, and had at least 1 postdose plasma concentration of brensocatib. 'Subjects analysed' included those adult participants who were evaluable for this endpoint. Here, 'n' signifies number of adult participants analysed for this endpoint.

End point type	Secondary

End point timeframe:

2 hours (h) post-dose on Day 1; Pre-dose and 2 h post-dose at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 40; Pre-dose at Weeks 16 and 52

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

End point values	Brensocatib 10 mg	Brensocatib 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	208		
Units: nanograms per milliliter (ng/ml)				
geometric mean (geometric coefficient of variation)				
Day 1: 2 h post-dose (n=18,24)	40.52 (± 69.1)	134.9 (± 51.4)		
Week 4: Pre-dose (n=56,63)	52.60 (± 68.7)	157.4 (± 70.8)		
Week 4: 2 h post-dose (n=20,25)	100.5 (± 32.8)	293.6 (± 35.1)		
Week 16: Pre-dose (n=94,105)	45.19 (± 55.0)	131.6 (± 69.0)		
Pre-dose at Week 28 (n=120,130)	49.30 (± 63.9)	143.0 (± 64.6)		
Week 28: 2 h post-dose (n=40,36)	91.79 (± 45.3)	323.7 (± 40.1)		
Week 40: Pre-dose (n=164,176)	45.71 (± 54.2)	136.8 (± 63.4)		
Week 40: 2 h post-dose (n=47,43)	107.3 (± 45.0)	302.6 (± 40.7)		
Week 52: Pre-dose (n=194,208)	45.78 (± 61.7)	135.4 (± 60.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Brensocatib in Adults (PK Substudy)

End point title	Plasma Concentration of Brensocatib in Adults (PK

End point description:

PK Concentration Analysis Set included adult participants who consented to participate in the PK substudy and received at least 1 dose of brensocatib, and had at least 1 postdose plasma concentration of brensocatib. 'Subjects analysed' included those adult participants who were evaluable for this endpoint. Here, 'n' signifies number of adult participants analysed for this endpoint.

End point type	Secondary

End point timeframe:

0.5 h, 2 h, and 4 to 8 h post-dose on Day 1and at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 48; Pre-dose at Weeks 16 and 52

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

End point values	Brensocatib 10 mg	Brensocatib 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: ng/ml				
geometric mean (geometric coefficient of variation)				
Day 1: 0.5 h post-dose (n=62,64)	34.51 (± 97.9)	85.13 (± 103.5)		
Day 1: 2 h post-dose (n=62,64)	44.52 (± 55.0)	120.0 (± 56.2)		
Day 1: 4-8 h post-dose (n=61,64)	38.13 (± 52.9)	108.5 (± 46.9)		
Week 4: Pre-dose (n=60,60)	57.53 (± 53.4)	131.3 (± 60.2)		
Week 4: 2 h post-dose (n=59,61)	100.3 (± 44.1)	286.7 (± 38.4)		
Week 16: Pre-dose (n=61,58)	50.24 (± 58.1)	138.0 (± 64.5)		
Week 28: Pre-dose (n=61,59)	50.33 (± 54.7)	124.6 (± 59.8)		
Week 28: 0.5 h post-dose (n=56,55)	89.75 (± 46.0)	235.5 (± 53.3)		
Week 28: 2 h post-dose (n=58,58)	95.33 (± 35.3)	271.9 (± 46.0)		
Week 28: 4-8 h post-dose (n=56,53)	86.27 (± 40.7)	246.4 (± 43.7)		
Week 40: Pre-dose (n=58,55)	51.80 (± 54.4)	119.3 (± 51.3)		
Week 40: 2 h post-dose (n=57,56)	93.74 (± 32.1)	271.2 (± 45.0)		
Week 52: Pre-dose (n=52,50)	49.93 (± 72.2)	131.6 (± 56.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Brensocatib in Adolescents (Main Study)

End point title	Plasma Concentration of Brensocatib in Adolescents (Main Study)[15]

End point description:

PK Concentration Analysis Set included adolescent participants who consented to participate in the main study and received at least 1 dose of brensocatib, and had at least 1 postdose plasma concentration of brensocatib.'Subjects analysed' included those adolescent participants who were evaluable for this endpoint. Here, 'n' signifies number of adolescent participants analysed for this endpoint.

End point type	Secondary

End point timeframe:

0.5 h, 2 h, and 4 to 8 h post-dose on Day 1 and at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 48; Pre-dose at Weeks 16 and 52

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

End point values	Brensocatib 10 mg	Brensocatib 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	16		
Units: ng/ml				
geometric mean (geometric coefficient of variation)				
Day 1: 0.5 h post-dose (n=12,14)	63.20 (± 51.7)	109.3 (± 139.1)		

Day 1: 2 h post-dose (n=13,14)	68.33 (± 32.5)	202.5 (± 50.7)		
Day 1: 4-8 h post-dose (n=12,14)	56.07 (± 24.1)	196.1 (± 52.4)		
Week 4: Pre-dose (n=14,16)	44.10 (± 64.2)	126.6 (± 90.4)		
Week 4: 2 h post-dose (n=13,16)	134.9 (± 52.8)	432.9 (± 44.3)		
Week 16: Pre-dose (n=14,15)	40.62 (± 51.6)	158.1 (± 95.7)		
Week 28: Pre-dose (n=14,11)	43.74 (± 57.2)	132.9 (± 96.3)		
Week 28: 0.5 h post-dose (n=11,10)	123.4 (± 49.1)	321.6 (± 93.8)		
Week 28: 2 h post-dose (n=13,10)	118.5 (± 30.5)	336.9 (± 77.7)		
Week 28: 4-8 h post-dose (n=11,10)	115.4 (± 27.7)	309.9 (± 48.0)		
Week 40: Pre-dose (n=10,7)	37.30 (± 52.5)	84.39 (± 102.3)		
Week 40: 2 h post-dose (n=10,7)	110.4 (± 43.9)	262.8 (± 77.6)		
Week 52: Pre-dose (n=6,7)	43.02 (± 64.8)	104.0 (± 57.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 56	
Adverse event reporting additional description:	
The safety analysis set included all participants who were randomised and received at least 1 dose of brensocatib or placebo.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Brensocatib 10 mg
Reporting group description:	
Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.	
Reporting group title	Brensocatib 25 mg
Reporting group description:	
Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.	

Serious adverse events	Brensocatib 10 mg	Placebo	Brensocatib 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 582 (17.35%)	108 / 563 (19.18%)	97 / 574 (16.90%)
number of deaths (all causes)	2	8	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Brain neoplasm			

subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Colon cancer			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Colorectal cancer			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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 melanoma			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign salivary gland neoplasm			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Mantle cell lymphoma			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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			
Hypotension			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Hypertension			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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			
Pyrexia			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Ovarian cyst			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic organ prolapse			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Uterovaginal prolapse			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	47 / 582 (8.08%)	67 / 563 (11.90%)	48 / 574 (8.36%)
occurrences causally related to treatment / all	0 / 69	1 / 107	0 / 65
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute respiratory failure			

subjects affected / exposed	2 / 582 (0.34%)	2 / 563 (0.36%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Eosinophilic pneumonia			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	3 / 582 (0.52%)	6 / 563 (1.07%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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 opacity			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Respiratory failure			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Pneumothorax spontaneous			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Pulmonary arterial hypertension			

subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 582 (0.34%)	2 / 563 (0.36%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Nasal polyps			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Device malfunction			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
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 sediment abnormal			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Weight decreased			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
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			
Alcohol poisoning			
subjects affected / exposed	1 / 582 (0.17%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Cervical vertebral fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Clavicle fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Fall			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Femur fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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

Fibula fracture			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Foreign body in throat			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Joint dislocation			
subjects affected / exposed	2 / 582 (0.34%)	0 / 563 (0.00%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Lower limb fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Meniscus injury			
subjects affected / exposed	2 / 582 (0.34%)	0 / 563 (0.00%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			

subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Pelvic fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Rib fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Road traffic accident			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper limb fracture			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Radius fracture			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	2 / 582 (0.34%)	4 / 563 (0.71%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
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 failure acute			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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 failure			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
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 arrest			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Atrioventricular block			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Pericardial effusion			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Myocardial infarction			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Coronary artery disease			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Diastolic dysfunction			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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			
Ischaemic stroke			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Loss of consciousness			

subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Presyncope			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Sciatica			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Glaucoma			

subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Cataract			
subjects affected / exposed	1 / 582 (0.17%)	3 / 563 (0.53%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness transient			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Vitreous haemorrhage			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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			
Rectal haemorrhage			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 582 (0.00%)	2 / 563 (0.36%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			

subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malabsorption			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Intestinal obstruction			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Dysphagia			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Femoral hernia incarcerated			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary cyst			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
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 and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Skin ulcer			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Urticaria			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Hydronephrosis			

subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Mobility decreased			

subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Muscle spasms			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Polymyalgia rheumatica			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Synovitis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Appendicitis			

subjects affected / exposed	2 / 582 (0.34%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Bronchitis fungal			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Herpes zoster			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	2 / 574 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis cryptosporidial			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Endophthalmitis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Diverticulitis			

subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	1 / 582 (0.17%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 582 (0.17%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	4 / 582 (0.69%)	6 / 563 (1.07%)	9 / 574 (1.57%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burkholderia gladioli infection			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 582 (0.34%)	1 / 563 (0.18%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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			

subjects affected / exposed	11 / 582 (1.89%)	16 / 563 (2.84%)	13 / 574 (2.26%)
occurrences causally related to treatment / all	0 / 13	0 / 19	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia aspiration			
subjects affected / exposed	0 / 582 (0.00%)	2 / 563 (0.36%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia necrotising			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	2 / 574 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Klebsiella infection			

subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Scrub typhus			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Sepsis			
subjects affected / exposed	1 / 582 (0.17%)	1 / 563 (0.18%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	2 / 582 (0.34%)	0 / 563 (0.00%)	0 / 574 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Urinary tract infection			
subjects affected / exposed	1 / 582 (0.17%)	1 / 563 (0.18%)	2 / 574 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			

subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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 pseudomonal			
subjects affected / exposed	0 / 582 (0.00%)	0 / 563 (0.00%)	1 / 574 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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
Pseudomonas infection			
subjects affected / exposed	2 / 582 (0.34%)	2 / 563 (0.36%)	2 / 574 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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
Viral pharyngitis			
subjects affected / exposed	1 / 582 (0.17%)	0 / 563 (0.00%)	0 / 574 (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 / 582 (0.00%)	1 / 563 (0.18%)	0 / 574 (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

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

Non-serious adverse events	Brensocatib 10 mg	Placebo	Brensocatib 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 582 (33.85%)	203 / 563 (36.06%)	213 / 574 (37.11%)
Nervous system disorders			
Headache			
subjects affected / exposed	39 / 582 (6.70%)	39 / 563 (6.93%)	49 / 574 (8.54%)
occurrences (all)	99	41	91
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 582 (7.04%)	36 / 563 (6.39%)	35 / 574 (6.10%)
occurrences (all)	55	39	41
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 582 (2.23%)	35 / 563 (6.22%)	17 / 574 (2.96%)
occurrences (all)	14	35	17
Infections and infestations			
COVID-19			
subjects affected / exposed	89 / 582 (15.29%)	83 / 563 (14.74%)	113 / 574 (19.69%)
occurrences (all)	93	88	119
Nasopharyngitis			
subjects affected / exposed	45 / 582 (7.73%)	43 / 563 (7.64%)	36 / 574 (6.27%)
occurrences (all)	53	54	52
Urinary tract infection			
subjects affected / exposed	27 / 582 (4.64%)	33 / 563 (5.86%)	30 / 574 (5.23%)
occurrences (all)	29	43	40

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2021	The following changes were made as per amendment 01: • Inclusion criteria: CT scan should be high-resolution; require males to use condoms; define "highly effective contraception" and clarify role of Investigator and designee in explaining contraception to participant. • Exclusion criteria: add CDC definition of "current smoker"; add exceptions to chronic use of oral steroids; clarify compliance with eDiary entries during Screening; exclude participants with hypersensitivity to brensocatib or its excipients. • Dosing may be interrupted for safety reasons.
07 December 2021	The following changes were made as per amendment 02: • Randomize approximately 40 adolescents (≥12 to <18 years of age) in a 2:2:1 ratio to brensocatib 10 mg, brensocatib 25 mg, or placebo (no stratification applied); add supportive toxicology and dose justification information, entry criteria, and pregnancy testing requirements for adolescents; add adolescents not required to provide sputum sample at any time during study if unable; add collection of blood PK and sputum PD samples from all adolescents. • Secondary objectives and/or endpoints: o Change from baseline in post-bronchodilator FEV1 is at Week 52 o Rate of severe PEs is based on adjudicated events o QOL-B is assessed in adults only o Remove physical exam as a safety endpoint parameter o Add evaluation of brensocatib exposure in adults and adolescents • Revise, combine, remove, and add exploratory objectives and/or endpoints, including addition of PGI-S and PGI-C in adults and QOL-PCD in adolescents. • Expand randomization enforcement criteria to restrict the percentage of participants with eosinophil count >300/mm3 and COPD comorbidity; add regional enrollment targets. • Inclusion criteria: clarify BMI threshold is for adults. • Exclusion criteria: clarify chronic antibiotic treatment of at least 3 months is before Screening; clarify PO steroids for any reason are prohibited; modify LFT thresholds to exclude Child-Pugh class C and remove separate criterion for Child-Pugh class B or C; clarify exclusion of attenuated vaccine is within 4 weeks before Screening; clarify participants currently treated for periodontal disease are excluded; clarify eDiary compliance assessment is for adults and as determined by the Investigator. • Independent adjudication committee adjudicates all PEs. • Clarify BEST completed by adults and EQ-5D-5L completed by adults and adolescents. • Protocol-defined PEs reported as AEs only if they fulfill a seriousness criterion; PEs do not fall under the other infection AESI category.
09 August 2022	The following change was made as per Amendment 03: • Add estimand framework. • Replace participants from Ukraine whose data will be listed and not included in formal efficacy and safety analyses. • Add PK sample collections from all adults enrolled in the study and sputum PD samples collections from all newly enrolled adults. • Exclude participants receiving cyclic antibiotics from PK/PD substudy. • Adjust criteria by which randomization is enforced. • Adjust enrollment targets and percentage of overall randomized population that any given country may contribute (Protocol Memorandum, 19 September 2022).

13 February 2024	The following changes were made as per Amendment 04: • Updated the interval duration for defining a separate PE (ie, at least 2 weeks [14 days] must occur between the end date of an earlier PE and the start date of the next PE). • Update multiplicity analysis methods for primary and secondary endpoints. • Clarify analysis for adult-only subgroup. • Add age group (adult, adolescent) as potential covariate in primary analysis model for primary endpoint. • Remove safety estimand (analysis unchanged). • Increase upper limit of enrollment target for North America, Western Europe Asia Pacific, and Latin America and enrollment cap for any single country (except the US).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported