Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis - The Willow Study

Summary

EudraCT number	2017-002533-32
Trial protocol	GB DE DK SE ES NL BG PL BE IT
Global end of trial date	12 December 2019

Results information

Result version number	v2 (current)
This version publication date	15 April 2023
First version publication date	23 December 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	INS1007-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03218917
WHO universal trial number (UTN)	-

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, medicalinformation@Insmed.com
Scientific contact	Insmed Medical Information, Insmed Incorporated, medicalinformation@Insmed.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	08 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2019
Global end of trial reached?	Yes
Global end of trial date	12 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the effect of brensocatib compared with placebo on time to first pulmonary exacerbation over the 24-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	31 October 2017
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	Netherlands: 7
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	New Zealand: 29
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	256
EEA total number of subjects	86

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)	106
From 65 to 84 years	150
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the trial at 116 sites in 14 countries from 31 October 2017 to 12 December 2019.

Pre-assignment

Screening details:

416 subjects were screened with 160 subjects resulting in a screen failure. A total of 256 subjects were randomized.

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:

Subjects received brensocatib 10 mg once daily before breakfast, for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Brensocatib
Investigational medicinal product code	
Other name	INS1007
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets administered orally.

Arm title	Brensocatib 25 mg

Arm description:

Subjects received brensocatib 25 mg once daily before breakfast, for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Brensocatib
Investigational medicinal product code	
Other name	INS1007
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets administered orally.

Arm title	Placebo

Arm description:

Subjects received the matching placebo once daily before breakfast, for 24 weeks.

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:
Matching placebo tablet administered orally.

Number of subjects in period 1	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
Started	82	87	87
Completed	76	75	74
Not completed	6	12	13
Adverse event, serious fatal	-	1	-
Reason Missing	-	2	-
Consent withdrawn by subject	2	4	10
Physician decision	-	1	1
Adverse event, non-fatal	3	3	2
Non-compliance of study drug	-	1	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Brensocatib 10 mg
Reporting group description:	
Subjects received brensocatib 10 mg once daily before breakfast, for 24 weeks.	
Reporting group title	Brensocatib 25 mg
Reporting group description:	
Subjects received brensocatib 25 mg once daily before breakfast, for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received the matching placebo once daily before breakfast, for 24 weeks.	

Reporting group values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
Number of subjects	82	87	87
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	64.6	63.7	64.0
standard deviation	± 12.42	± 12.67	± 11.86
Gender categorical Units: Subjects			
Female	57	62	55
Male	25	25	32
Race Units: Subjects			
Caucasian (White)	76	78	71
African American/Black of African origin	0	2	2
Asian	5	5	13
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1	1	1
Other	0	1	0
Ethnicity Units: Subjects			
Not Hispanic or Latino	80	83	87
Hispanic or Latino	2	4	0

Reporting group values	Total		
Number of subjects	256		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	174		
Male	82		
Race Units: Subjects			
Caucasian (White)	225		
African American/Black of African origin	4		
Asian	23		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	3		
Other	1		
Ethnicity Units: Subjects			
Not Hispanic or Latino	250		
Hispanic or Latino	6		

End points

End points reporting groups

Reporting group title	Brensocatib 10 mg
Reporting group description:	
Subjects received brensocatib 10 mg once daily before breakfast, for 24 weeks.	
Reporting group title	Brensocatib 25 mg
Reporting group description:	
Subjects received brensocatib 25 mg once daily before breakfast, for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received the matching placebo once daily before breakfast, for 24 weeks.	
Subject analysis set title	Brensocatib 10 mg (Pharmacodynamic [PD] population)
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received brensocatib 10 mg once daily before breakfast for 24 weeks. PD population: All subjects who received at least 1 dose of study treatment, had at least 1 predose and 1 postdose measurement for neutrophil elastase (NE), or proteinase 3, or cathepsin G, or other biomarkers, and had no major protocol deviations considered to impact the analysis of PD data. 1 subject who was randomized to received brensocatib 10 mg also received brensocatib 25 mg. This subject is excluded from the brensocatib 10 mg PD population and included in brensocatib 25 mg PD population.	
Subject analysis set title	Brensocatib 25 mg (Pharmacodynamic [PD] population)
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received brensocatib 25 mg once daily before breakfast for 24 weeks. PD population: All subjects who received at least 1 dose of study treatment, had at least 1 predose and 1 postdose measurement for neutrophil elastase (NE), or proteinase 3, or cathepsin G, or other biomarkers, and had no major protocol deviations considered to impact the analysis of PD data. 1 subject who was randomized to receive brensocatib 10 mg and 1 subject who was randomized to received placebo, also received brensocatib 25 mg. Both subjects are included in brensocatib 25 mg PD population and are excluded from brensocatib 10 mg and placebo PD populations.	
Subject analysis set title	Placebo (Pharmacodynamic [PD] population)
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received the matching placebo once daily before breakfast for 24 weeks. PD population: All subjects who received at least 1 dose of study treatment, had at least 1 predose and 1 postdose measurement for neutrophil elastase (NE), or proteinase 3, or cathepsin G, or other biomarkers, and had no major protocol deviations considered to impact the analysis of PD data. 1 subject who was randomized to received placebo also received brensocatib 25 mg. The subject is excluded from the placebo PD population and included in brensocatib 25 mg PD population.	

Primary: Time to the first pulmonary exacerbation over 24-week treatment period

End point title	Time to the first pulmonary exacerbation over 24-week treatment period
End point description:	
Pulmonary exacerbation was defined as having 3 or more of the following 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 minimum of 4 weeks must have occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 4 weeks from the prior exacerbation was not considered a new exacerbation. The median time to first exacerbation could not be estimated for brensocatib 10 mg or brensocatib 25 mg. 99999 = The median, upper and lower limit of confidence interval (CI) was not estimated due to insufficient number of participants with exacerbations in the groups.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[1]	29[2]	42[3]	
Units: Days				
median (confidence interval 90%)	99999 (99999 to 99999)	99999 (99999 to 99999)	189.0 (141.0 to 99999)	

Notes:

[1] - Subjects with at least one exacerbation.

[2] - Subjects with at least one exacerbation.

[3] - Subjects with at least one exacerbation.

Statistical analyses

Statistical analysis title	Brensocatib 10 mg vs Placebo
Comparison groups	Brensocatib 10 mg v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Stratified Log-rank test

Statistical analysis title	Brensocatib 25 mg vs Placebo
Comparison groups	Brensocatib 25 mg v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Stratified Log-rank test

Secondary: Change from baseline in Quality of Life Questionnaire – Bronchiectasis (QOL-B) respiratory symptoms domain score over 24 week treatment period

End point title	Change from baseline in Quality of Life Questionnaire – Bronchiectasis (QOL-B) respiratory symptoms domain score over 24 week treatment period

End point description:

The QOL-B is a validated, self-administered patient reported outcome (PRO) that assesses symptoms, functioning, and health-related (HR) QOL for subjects with non-cystic fibrosis bronchiectasis (NCFBE). The QOL-B contains 37 items in 8 domains (Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions and Treatment Burden). Each of the 37 items is scored from 1 to 4, and each of the 8 domains scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HR QoL. A positive change from baseline indicates improvement in symptoms. For this outcome measure, the respiratory symptoms domain score was reported. The analysis was based on mixed model for repeated measures (MMRM) approach. Number of subjects analysed are the number of subjects with data available for analyses at the latest assessment visit over the 24-week treatment period.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	77	72	
Units: Score on a scale				
least squares mean (standard error)	3.8 (± 0.78)	5.9 (± 0.76)	5.7 (± 0.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from screening in post-bronchodilator percent predicted forced expiratory volume in 1 second (ppFEV1) over 24-week treatment period

End point title	Change from screening in post-bronchodilator percent predicted forced expiratory volume in 1 second (ppFEV1) over 24-week treatment period

End point description:

FEV1 was used to assess lung function and is the maximum amount of air that can be forced out in one second after taking a deep breath. The percent predicted FEV1 was calculated by converting the spirometer reading to a percentage of what would be predicted as normal FEV1 based on a several personal factors (e.g. sex, age, etc.). Change from screening in percent predicted FEV1 to Week 24 was calculated as: percent predicted FEV1 value at Week 24 and percent predicted FEV1 value at screening. A positive percent change from screening indicates an improvement in lung function. The analysis was done using analysis of covariance (ANCOVA) with Pa colonization status and maintenance macrolide antibiotic use at Baseline as covariates. Number of subjects analysed are the number of subjects with data available for analyses over the 24-week treatment period.

End point type	Secondary

End point timeframe:

Screening to Week 24

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	73	
Units: percent predicted FEV1				
least squares mean (standard error)	-0.3 (± 0.88)	-0.3 (± 0.85)	-1.8 (± 0.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in concentration of active neutrophil elastase (NE) in sputum

End point title	Change from baseline in concentration of active neutrophil elastase (NE) in sputum

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Brensocatib 10 mg (Pharmacodynamic [PD] population)	Brensocatib 25 mg (Pharmacodynamic [PD] population)	Placebo (Pharmacodynamic [PD] population)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	89	84	
Units: µg/mL				
least squares mean (standard error)	-2.928 (± 0.351)	-4.117 (± 0.322)	-1.409 (± 0.313)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who experienced a pulmonary exacerbation

End point title	Number of subjects who experienced a pulmonary exacerbation

End point description:

Pulmonary exacerbation was defined as having 3 or more of the following 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 minimum of 4 weeks must of occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 4 weeks from the prior exacerbation was not considered a new exacerbation.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Brensocatib 10 mg	Brensocatib 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	87	87	
Units: Subjects	26	29	42	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 28 (End of study visit)

Adverse event reporting additional description:

Safety population included all subjects who received at least one dose of study treatment. 2 subjects who were randomised to placebo and Brensocatib 10 mg group received Brensocatib 25 mg and hence were included in the Brensocatib 25 mg group in the Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Brensocatib 10 mg (Safety population)

Reporting group description:

Subjects received brensocatib 10 mg once daily before breakfast for 24 weeks. Safety population: All subjects who received at least one dose of study treatment. 1 subject who was randomized to receive brensocatib 10 mg also received brensocatib 25 mg. This subject is excluded from the brensocatib 10 mg safety population and included in brensocatib 25 mg safety population.

Reporting group title	Placebo (Safety population)

Reporting group description:

Subjects received the matching placebo once daily before breakfast, for 24 weeks. Safety population: All subjects who received at least one dose of study treatment. 1 subject who was randomized to receive placebo also received brensocatib 25 mg. The subject is excluded from the placebo safety population and included in brensocatib 25 mg safety population. 1 subject who was randomized to receive placebo left the trial before receiving study treatment and is also excluded from the placebo safety population.

Reporting group title	Brensocatib 25 mg (Safety population)

Reporting group description:

Subjects received brensocatib 25 mg once daily before breakfast, for 24 weeks. Safety population: All subjects who received at least one dose of study treatment. 1 subject who was randomized to receive brensocatib 10 mg and 1 subject who was randomized to received placebo, also received brensocatib 25 mg. Both subjects are included in brensocatib 25 mg safety population and are excluded from brensocatib 10 mg and placebo safety populations.

Serious adverse events	Brensocatib 10 mg (Safety population)	Placebo (Safety population)	Brensocatib 25 mg (Safety population)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 81 (13.58%)	19 / 85 (22.35%)	10 / 89 (11.24%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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			

Haemoptysis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 85 (2.35%)	0 / 89 (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
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 85 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 85 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung infiltration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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			
Ventricular extrasystoles			

subjects affected / exposed	0 / 81 (0.00%)	0 / 85 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 81 (1.23%)	1 / 85 (1.18%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Carotid artery occlusion			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Blood and lymphatic system disorders			
Lymphocytosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 81 (0.00%)	0 / 85 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 81 (0.00%)	0 / 85 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (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			
Biliary colic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (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			
Foot deformity			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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			
Pneumonia			
subjects affected / exposed	0 / 81 (0.00%)	3 / 85 (3.53%)	4 / 89 (4.49%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	5 / 81 (6.17%)	9 / 85 (10.59%)	4 / 89 (4.49%)
occurrences causally related to treatment / all	1 / 7	1 / 10	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Aspergilloma			

subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	0 / 89 (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 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (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
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	0 / 89 (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 (Safety population)	Placebo (Safety population)	Brensocatib 25 mg (Safety population)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 81 (58.02%)	33 / 85 (38.82%)	43 / 89 (48.31%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 81 (2.47%)	5 / 85 (5.88%)	1 / 89 (1.12%)
occurrences (all)	2	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 81 (9.88%)	3 / 85 (3.53%)	12 / 89 (13.48%)
occurrences (all)	11	4	16
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	3 / 81 (3.70%)	6 / 85 (7.06%)	7 / 89 (7.87%)
occurrences (all)	3	6	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 81 (6.17%)	9 / 85 (10.59%)	3 / 89 (3.37%)
occurrences (all)	5	12	3
Periodontal disease			
subjects affected / exposed	2 / 81 (2.47%)	0 / 85 (0.00%)	5 / 89 (5.62%)
occurrences (all)	2	0	5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 81 (3.70%)	2 / 85 (2.35%)	8 / 89 (8.99%)
occurrences (all)	3	2	9
Cough			
subjects affected / exposed	15 / 81 (18.52%)	10 / 85 (11.76%)	12 / 89 (13.48%)
occurrences (all)	16	11	14
Sputum increased			
subjects affected / exposed	9 / 81 (11.11%)	6 / 85 (7.06%)	9 / 89 (10.11%)
occurrences (all)	11	7	10
Haemoptysis			
subjects affected / exposed	6 / 81 (7.41%)	1 / 85 (1.18%)	2 / 89 (2.25%)
occurrences (all)	8	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 81 (7.41%)	1 / 85 (1.18%)	1 / 89 (1.12%)
occurrences (all)	6	1	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 81 (7.41%)	4 / 85 (4.71%)	4 / 89 (4.49%)
occurrences (all)	6	4	4
Sinusitis			
subjects affected / exposed	5 / 81 (6.17%)	6 / 85 (7.06%)	4 / 89 (4.49%)
occurrences (all)	5	7	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2018	The amendment included the following changes: * Added description of healthy volunteer studies to Introduction * Added text to align Study Objectives with Study Endpoints * Added 2 weeks to the Screening Period (from 4 to 6 weeks) in order to accommodate additional dental screening and clearning procedures * Added urine samples for biomarker assessment and pregnancy test * Clarified acceptable contraception procedures * Added exclusion for Papillon-Lefvre syndrome * Added that subjects who discontinued for adverse event (AE) were followed to resolution or stabilization * Added physical examination, CRP and prothrombin time tests, collection of pharmacokinetic (PK) sample timing to Schedule of Assessments * Added details to the sample size determination
27 April 2018	The amendment included the following changes: * Clarified the duration of AE collection * Provided ±3 day window for data collection after discontinuation for AE and a ±3 day window allowance for study visits
24 September 2018	The amendment included the following changes: * Updated contact for Regulatory Affairs personnel * Specified that Data Monitoring Committee (DMC) members would review data in semi-blinded or unblinded manner at predetermined intervals * Added chest computed tomography (CT) scan for subjects whose past radiographic image records were not available * Aligned study days in Study Schematic with Schedule of Assessments * Revised to state that subjects could not undergo sputum induction procedure during Screening; subjects unable to produce sputum at Screening was considered a screen failure * Revised to state that any subject with pulmonary exacerbation requiring antibiotics after Screening and before randomization was a screen failure * Clarified that subjects with hypothyroidism currently treated with thyroid-stimulating hormone (TSH), and whose T3/T4 levels were within normal range were eligible for enrollment in the trial * Clarified enrollment eligibility for subjects who required repeat electrocardiogram (ECG) and or pulmonary function tests that were not deemed clinically significant * Clarified that subjects who were edentulous still received a dental examination to check for sores caused by dentures * Added requirement that subjects complete PRO questionnaires prior to first dose of study drug * Added meal time for subjects in the Intense PK Population * Added Child-Pugh Score for subjects with abnormal liver function tests * Added sparse PK sampling for subjects at all sites with processing ability * Added calculation of neutrophil elastase method * Added literature references

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported