



Clinical trial results:

A multicentre, randomised, double-blind, placebo-controlled phase 2 trial to evaluate efficacy and safety of lenabasum in cystic fibrosis

Summary

EudraCT number	2017-003723-29
Trial protocol	GB DE HU SE FR PT SK AT BE ES BG NL CZ GR PL IT RO
Global end of trial date	17 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 January 2022
First version publication date	20 January 2022

Trial information

Trial identification

Sponsor protocol code	JBT101-CF-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03451045
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Corbus Pharmaceuticals Inc.
Sponsor organisation address	500 River Ridge Drive, Norwood, United States, MA 02062
Public contact	Corbus General Information, Corbus Pharmaceuticals Inc., +1 617-963-0100, info@corbuspharma.com
Scientific contact	Corbus General Information, Corbus Pharmaceuticals Inc., +1 617-963-0100, info@corbuspharma.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	10 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2020
Global end of trial reached?	Yes
Global end of trial date	17 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lenabasum 20 mg twice per day (BID) compared to placebo in the treatment of cystic fibrosis (CF) by assessing the rate of pulmonary exacerbations (PEX) using this study's primary definition of new PEX (the physician diagnosis of PEX, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEX, and met at least 4 of 12 Fuch's criteria).

Protection of trial subjects:

Oversight of subject safety in this trial was provided by a data monitoring committee (DMC) subcommittee of the Cystic Fibrosis Foundation Therapeutics Data Safety Monitoring Board, an independent group of CF experts that was to advise the Sponsor. The primary responsibilities of the DMC were to: 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy; and 2) make recommendations to the Sponsor concerning the continuation, modification, or termination of the trial.

Background therapy:

Each patient was maintained on all his/her baseline medications for CF from screening through Visit 9, unless the investigator or treating physician judged a change in therapy was needed to provide best medical care for the patient.

Evidence for comparator:

This was a placebo-controlled trial. All patients in the trial maintained their previous CF medication in addition to randomised study medication.

Actual start date of recruitment	14 February 2018
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	United States: 151
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 35

Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 18
Worldwide total number of subjects	447
EEA total number of subjects	211

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)	85
Adults (18-64 years)	361
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 08 May 2018 and 08 November 2019 (211 in Europe and 236 outside Europe).

Pre-assignment

Screening details:

A total of 541 patients were screened and of these 447 were randomised, including 425 patients treated and 22 randomised but not treated.

Period 1

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

Blinding implementation details:

Lenabasum and placebo capsules had similar physical appearance and were packaged, labelled and handled so that patients and site staff were not able to distinguish treatments.

Arms

Are arms mutually exclusive?	No
Arm title	Lenabasum 20 mg

Arm description:

Randomised treatment arm, in which patients were treated with the higher dose of lenabasum.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg Lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)

Arm title	Lenabasum 5 mg
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Arm description:

Randomised treatment arm, in which patients were treated with the lower dose of lenabasum.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg lenabasum , taken orally twice daily (total dose: 10 mg lenabasum per day)

Arm title	Placebo
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Arm description:

Randomised treatment arm, in which patients were treated with placebo.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Placebo matching lenabasum capsules administered twice daily.	
Arm title	Lenabasum 20 mg age <18
Arm description:	
Patients aged <18 years in the lenabasum 20 mg treatment group	
Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
20 mg lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)	
Arm title	Lenabasum 5 mg age <18
Arm description:	
Patients aged <18 years in the lenabasum 5 mg treatment group	
Arm type	Experimental
Investigational medicinal product name	Lenabasum 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
5 mg Lenabasum, taken orally twice daily (total dose: 10 mg lenabasum per day)	
Arm title	Placebo <18
Arm description:	
Patients aged <18 years in the placebo treatment group	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Placebo matching lenabasum capsules administered twice daily.	
Arm title	Lenabasum 20 mg age >=18
Arm description:	
Patients aged >=18 years in the lenabasum 20 mg treatment group	
Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg lenabasum , taken orally twice daily (total dose: 40 mg lenabasum per day)

Arm title	Lenabasum 5 mg age >=18
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Arm description:

Patients aged >=18 years in the lenabasum 5 mg treatment group

Arm type	Experimental
Investigational medicinal product name	Lenabasum 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg Lenabasum, taken orally twice daily (total dose: 10 mg lenabasum per day)

Arm title	Placebo >=18
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Arm description:

Patients aged >=18 years in the placebo treatment group

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

Dosage and administration details:

Placebo matching lenabasum capsules administered twice daily.

Number of subjects in period 1	Lenabasum 20 mg	Lenabasum 5 mg	Placebo
Started	165	89	171
Completed	148	85	154
Not completed	17	4	17
Physician decision	1	1	1
Consent withdrawn by subject	4	-	5
Adverse event, non-fatal	7	1	3
Not specified	-	-	3
Pregnancy	-	-	2
Non-compliance with study drug	-	-	-
Noncompliance with study drug	-	-	-
Lack of efficacy	3	2	2
Noncompliance	2	-	1

Number of subjects in period 1	Lenabasum 20 mg age <18	Lenabasum 5 mg age <18	Placebo <18
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Started	32	13	40
Completed	29	13	36
Not completed	3	0	4
Physician decision	-	-	1
Consent withdrawn by subject	2	-	2
Adverse event, non-fatal	-	-	1
Not specified	-	-	-
Pregnancy	-	-	-
Non-compliance with study drug	1	-	-
Noncompliance with study drug	-	-	-
Lack of efficacy	-	-	-
Noncompliance	-	-	-

Number of subjects in period 1	Lenabasum 20 mg age ≥18	Lenabasum 5 mg age ≥18	Placebo ≥18
Started	133	76	131
Completed	119	72	118
Not completed	14	4	13
Physician decision	1	1	-
Consent withdrawn by subject	2	-	3
Adverse event, non-fatal	7	1	2
Not specified	-	-	3
Pregnancy	-	-	2
Non-compliance with study drug	-	-	-
Noncompliance with study drug	1	-	1
Lack of efficacy	3	2	2
Noncompliance	-	-	-

Baseline characteristics

Reporting groups^[1]

Reporting group title	Lenabasum 20 mg
Reporting group description:	
Randomised treatment arm, in which patients were treated with the higher dose of lenabasum.	
Reporting group title	Lenabasum 5 mg
Reporting group description:	
Randomised treatment arm, in which patients were treated with the lower dose of lenabasum.	
Reporting group title	Placebo
Reporting group description:	
Randomised treatment arm, in which patients were treated with placebo.	
Reporting group title	Lenabasum 20 mg age <18
Reporting group description:	
Patients aged <18 years in the lenabasum 20 mg treatment group	
Reporting group title	Lenabasum 5 mg age <18
Reporting group description:	
Patients aged <18 years in the lenabasum 5 mg treatment group	
Reporting group title	Placebo <18
Reporting group description:	
Patients aged <18 years in the placebo treatment group	
Reporting group title	Lenabasum 20 mg age ≥18
Reporting group description:	
Patients aged ≥18 years in the lenabasum 20 mg treatment group	
Reporting group title	Lenabasum 5 mg age ≥18
Reporting group description:	
Patients aged ≥18 years in the lenabasum 5 mg treatment group	
Reporting group title	Placebo ≥18
Reporting group description:	
Patients aged ≥18 years in the placebo treatment group	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The numbers of patients in the baseline period includes a total of 425 randomised and treated patients. Additional groups appearing for the baseline period were subgroups of this population according to age <18 or ≥18 years. Also, patients enrolled but not treated were not included.

Reporting group values	Lenabasum 20 mg	Lenabasum 5 mg	Placebo
Number of subjects	165	89	171
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			
Age at baseline (start of treatment period).			
Units: years			
arithmetic mean	26.2	28.9	26.6
standard deviation	± 9.08	± 11.24	± 10.81
Gender categorical			
Units: Subjects			
Female	91	44	93
Male	74	45	78
FEV1			
Forced expiratory volume in 1 second (FEV1), categorical: <70% predicted or ≥70% predicted at baseline.			
Units: Subjects			
<70% predicted	120	62	121
≥70% predicted	45	27	50
Pulmonary exacerbations (PEX)			
Number of previous PEX requiring antibiotics in the year before study entry			
Units: Subjects			
None	2	0	0
One	76	44	78
Two	57	30	68
Three	30	15	24
Four	0	0	1
FEV1			
FEV1 (L), at baseline.			
Units: litre(s)			
arithmetic mean	2.0947	2.2004	2.1659
standard deviation	± 0.73374	± 0.76964	± 0.78117

Reporting group values	Lenabasum 20 mg age <18	Lenabasum 5 mg age <18	Placebo <18
Number of subjects	32	13	40
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			
Age at baseline (start of treatment period).			
Units: years			
arithmetic mean	14.5	15.0	15.1
standard deviation	± 1.37	± 1.96	± 1.63
Gender categorical			
Units: Subjects			
Female	17	4	16

Male	15	9	24
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FEV1			
Forced expiratory volume in 1 second (FEV1), categorical: <70% predicted or ≥70% predicted at baseline.			
Units: Subjects			
<70% predicted	16	6	18
≥70% predicted	16	7	22
Pulmonary exacerbations (PEx)			
Number of previous PEx requiring antibiotics in the year before study entry			
Units: Subjects			
None	0	0	0
One	20	9	23
Two	8	1	14
Three	4	3	2
Four	0	0	1
FEV1			
FEV1 (L), at baseline.			
Units: litre(s)			
arithmetic mean	2.2749	2.4378	2.4551
standard deviation	± 0.68323	± 0.65759	± 0.76960

Reporting group values	Lenabasum 20 mg age ≥18	Lenabasum 5 mg age ≥18	Placebo ≥18
Number of subjects	133	76	131
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			
Age at baseline (start of treatment period).			
Units: years			
arithmetic mean	29.1	31.3	30.1
standard deviation	± 7.79	± 10.42	± 9.94
Gender categorical			
Units: Subjects			
Female	74	40	77
Male	59	36	54
FEV1			
Forced expiratory volume in 1 second (FEV1), categorical: <70% predicted or ≥70% predicted at baseline.			
Units: Subjects			
<70% predicted	104	56	103

>=70% predicted	29	20	28
Pulmonary exacerbations (PEx)			
Number of previous PEx requiring antibiotics in the year before study entry			
Units: Subjects			
None	2	0	0
One	56	35	55
Two	49	29	54
Three	26	12	22
Four	0	0	0
FEV1			
FEV1 (L), at baseline.			
Units: litre(s)			
arithmetic mean	2.0513	2.1598	2.0776
standard deviation	± 0.74128	± 0.78383	± 0.76598

Reporting group values	Total		
Number of subjects	425		
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			
Age at baseline (start of treatment period).			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	228		
Male	197		
FEV1			
Forced expiratory volume in 1 second (FEV1), categorical: <70% predicted or >=70% predicted at baseline.			
Units: Subjects			
<70% predicted	303		
>=70% predicted	122		
Pulmonary exacerbations (PEx)			
Number of previous PEx requiring antibiotics in the year before study entry			
Units: Subjects			
None	2		
One	198		
Two	155		
Three	69		

Four	1		
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FEV1			
FEV1 (L), at baseline.			
Units: litre(s)			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Modified ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat (mITT) population included all randomised subjects who received at least 1 dose of study drug, categorised by planned treatment.

Note: the mITT population was identical to the population of all treated patients.

Reporting group values	Modified ITT population		
Number of subjects	425		
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			
Age at baseline (start of treatment period).			
Units: years			
arithmetic mean	26.9		
standard deviation	± 25.0		
Gender categorical			
Units: Subjects			
Female	228		
Male	197		
FEV1			
Forced expiratory volume in 1 second (FEV1), categorical: <70% predicted or ≥70% predicted at baseline.			
Units: Subjects			
<70% predicted	303		
≥70% predicted	122		
Pulmonary exacerbations (PEX)			
Number of previous PEX requiring antibiotics in the year before study entry			
Units: Subjects			
None	2		

One	198		
Two	155		
Three	69		
Four	1		
FEV1			
FEV1 (L), at baseline.			
Units: litre(s)			
arithmetic mean	2.1455		
standard deviation	± 1.9880		

End points

End points reporting groups

Reporting group title	Lenabasum 20 mg
Reporting group description: Randomised treatment arm, in which patients were treated with the higher dose of lenabasum.	
Reporting group title	Lenabasum 5 mg
Reporting group description: Randomised treatment arm, in which patients were treated with the lower dose of lenabasum.	
Reporting group title	Placebo
Reporting group description: Randomised treatment arm, in which patients were treated with placebo.	
Reporting group title	Lenabasum 20 mg age <18
Reporting group description: Patients aged <18 years in the lenabasum 20 mg treatment group	
Reporting group title	Lenabasum 5 mg age <18
Reporting group description: Patients aged <18 years in the lenabasum 5 mg treatment group	
Reporting group title	Placebo <18
Reporting group description: Patients aged <18 years in the placebo treatment group	
Reporting group title	Lenabasum 20 mg age ≥18
Reporting group description: Patients aged ≥18 years in the lenabasum 20 mg treatment group	
Reporting group title	Lenabasum 5 mg age ≥18
Reporting group description: Patients aged ≥18 years in the lenabasum 5 mg treatment group	
Reporting group title	Placebo ≥18
Reporting group description: Patients aged ≥18 years in the placebo treatment group	
Subject analysis set title	Modified ITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The modified intention-to-treat (mITT) population included all randomised subjects who received at least 1 dose of study drug, categorised by planned treatment. Note: the mITT population was identical to the population of all treated patients.	

Primary: Rate of new pulmonary exacerbations - primary definition

End point title	Rate of new pulmonary exacerbations - primary definition ^[1]
End point description: The proportion of subjects with at least 1 PEx event at end of treatment, based on the primary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx, and meeting at least 4 of 12 Fuch's criteria).	
End point type	Primary
End point timeframe: Event rate at the end of treatment	
Notes:	

[1] - 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: The groups not included represent subgroups of the overall population including only patients aged less than 18 years or aged greater than or equal to 18 years.

End point values	Lenabasum 20 mg	Lenabasum 5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	89	171	
Units: Subjects	89	50	94	

Statistical analyses

Statistical analysis title	PEX rate: Lenabasum 20 mg vs placebo
Statistical analysis description:	
The event rate of new PEX was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Placebo v Lenabasum 20 mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.6178 ^[3]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	1.0624
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8375
upper limit	1.3478

Notes:

[2] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEX requiring IV antibiotics in the previous year, baseline CF transmembrane conductance regulator (CFTR) targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[3] - Lenabasum 20 mg vs placebo

Statistical analysis title	PEX rate: Lenabasum 5 mg vs placebo
Statistical analysis description:	
The event rate of new PEX was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Lenabasum 5 mg v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.427 ^[5]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.887

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6597
upper limit	1.1924

Notes:

[4] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[5] - Lenabasum 5 mg vs placebo

Primary: Rate of new pulmonary exacerbations in patients age ≥18 - primary definition

End point title	Rate of new pulmonary exacerbations in patients age ≥18 - primary definition ^[6]
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End point description:

The proportion of subjects aged ≥18 years with at least 1 PEx event at end of treatment, based on the primary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx, and meeting at least 4 of 12 Fuch's criteria).

End point type	Primary
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End point timeframe:

Event rate at the end of treatment

Notes:

[6] - 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: This represents a subgroup of the overall population including only patients aged greater than or equal to 18 years.

End point values	Lenabasum 20 mg age ≥18	Lenabasum 5 mg age ≥18	Placebo ≥18	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	76	131	
Units: Subjects aged ≥18 years	72	34	82	

Statistical analyses

Statistical analysis title	PEx rate: Lenabasum 20 mg vs placebo age ≥18
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Statistical analysis description:

The event rate of new PEx was compared between the lenabasum and placebo groups in patients aged ≥18 years. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.

Comparison groups	Lenabasum 20 mg age ≥18 v Placebo ≥18
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.9296 ^[8]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.9884

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7639
upper limit	1.2791

Notes:

[7] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[8] - Lenabasum 20 mg vs placebo in patients aged ≥18 years

Statistical analysis title	PEx rate: Lenabasum 5 mg vs placebo ag...
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Statistical analysis description:

The event rate of new PEx was compared between the lenabasum and placebo groups in patients aged ≥18 years. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.

Comparison groups	Placebo ≥18 v Lenabasum 5 mg age ≥18
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.2757 ^[10]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.8404
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6147
upper limit	1.1489

Notes:

[9] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[10] - Lenabasum 5 mg vs placebo in patients aged ≥18 years

Secondary: Rate of PEx - secondary definition

End point title	Rate of PEx - secondary definition ^[11]
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End point description:

The proportion of subjects with at least 1 PEx event, based on the secondary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx).

End point type	Secondary
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End point timeframe:

Event rate at the end of treatment

Notes:

[11] - 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: The groups not included represent subgroups of the overall population including only patients aged less than 18 years or aged greater than or equal to 18 years.

End point values	Lenabasum 20 mg	Lenabasum 5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	89	171	
Units: Subjects	99	56	107	

Statistical analyses

Statistical analysis title	PEX rate: Lenabasum 20 mg vs placebo
Statistical analysis description:	
The event rate of new PEX was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Lenabasum 20 mg v Placebo
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.7145 ^[13]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	1.0419
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8364
upper limit	1.2978

Notes:

[12] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEX requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[13] - Lenabasum 20 mg vs placebo

Statistical analysis title	PEX rate: Lenabasum 5 mg vs placebo
Statistical analysis description:	
The event rate of new PEX was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Lenabasum 5 mg v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.3797 ^[15]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.8851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.674
upper limit	1.1622

Notes:

[14] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[15] - Lenabasum 5 mg vs placebo

Secondary: Rate of new pulmonary exacerbations in patients age <18 - primary definition

End point title	Rate of new pulmonary exacerbations in patients age <18 - primary definition ^[16]
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End point description:

The proportion of subjects aged <18 years with at least 1 PEx event at end of treatment, based on the primary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx, and meeting at least 4 of 12 Fuch's criteria).

End point type	Secondary
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End point timeframe:

Event rate at the end of treatment

Notes:

[16] - 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: This represents a subgroup of the overall population including only patients aged less than 18 years.

End point values	Lenabasum 20 mg age <18	Lenabasum 5 mg age <18	Placebo <18	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	13	40	
Units: Subjects aged <18 years	17	5	12	

Statistical analyses

Statistical analysis title	PEx rate: Lenabasum 20 mg vs placebo
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Statistical analysis description:

The event rate of new PEx was compared between the lenabasum and placebo groups in patients aged <18 years. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.

Comparison groups	Lenabasum 20 mg age <18 v Placebo <18
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.17 ^[18]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	1.5496
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.829
upper limit	2.8965

Notes:

[17] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus >=70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[18] - Lenabasum 20 mg vs placebo in patients aged <18 years

Statistical analysis title	PEx rate: Lenabasum 5 mg vs placebo age <18
Statistical analysis description:	
The event rate of new PEx was compared between the lenabasum and placebo groups in patients aged <18 years. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Lenabasum 5 mg age <18 v Placebo <18
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.8789 ^[20]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.438
upper limit	2.6236

Notes:

[19] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus >=70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[20] - Lenabasum 5 mg vs placebo in patients aged <18 years

Secondary: Rate of PEx - secondary definition – age <18 years

End point title	Rate of PEx - secondary definition – age <18 years ^[21]
End point description:	
The proportion of subjects age <18 years with at least 1 PEx event, based on the secondary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx).	
End point type	Secondary
End point timeframe:	
Event rate at the end of treatment	

Notes:

[21] - 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: This represents a subgroup of the overall population including only patients aged less than 18 years.

End point values	Lenabasum 20 mg age <18	Lenabasum 5 mg age <18	Placebo <18	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	13	40	
Units: Subjects aged <18 years	21	7	15	

Statistical analyses

Statistical analysis title	PEx rate: Lenabasum 20 mg vs placebo – age <18
Statistical analysis description:	
The event rate of new PEx was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Lenabasum 20 mg age <18 v Placebo <18
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.172 ^[23]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	1.4377
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8539
upper limit	2.4209

Notes:

[22] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[23] - Lenabasum 20 mg vs placebo

Statistical analysis title	PEx rate: Lenabasum 5 mg vs placebo – age ≥18
Statistical analysis description:	
The event rate of new PEx was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Placebo <18 v Lenabasum 5 mg age <18
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	= 0.8897 ^[25]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.9463
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4334
upper limit	2.0661

Notes:

[24] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[25] - Lenabasum 5 mg vs placebo

Secondary: Rate of PEx - secondary definition – age ≥ 18

End point title	Rate of PEx - secondary definition – age ≥ 18 ^[26]
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End point description:

The proportion of subjects age ≥18 years with at least 1 PEx event, based on the secondary definition of PEx (physician diagnosis of PEx, treatment with new oral, intravenous, or inhaled antibiotic(s) starting >28 days after completion of the last course of antibiotics for a prior PEx).

End point type	Secondary
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End point timeframe:

Event rate at the end of treatment

Notes:

[26] - 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: This represents a subgroup of the overall population including only patients aged greater than or equal to 18 years.

End point values	Lenabasum 20 mg age ≥18	Lenabasum 5 mg age ≥18	Placebo ≥18	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	76	131	
Units: Subjects aged ≥ 18 years	78	49	92	

Statistical analyses

Statistical analysis title	PEx rate: Lenabasum 20 mg vs placebo – age ≥18
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Statistical analysis description:

The event rate of new PEx was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.

Comparison groups	Lenabasum 20 mg age ≥18 v Placebo ≥18
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.7062 ^[28]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.9548
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7505
upper limit	1.2146

Notes:

[27] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year,

baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[28] - Lenabasum 20 mg vs placebo

Statistical analysis title	PEx rate: Lenabasum 5 mg vs placebo - age ≥ 18
Statistical analysis description: The event rate of new PEx was compared between the lenabasum and placebo groups. The overall type I error rate was controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy.	
Comparison groups	Placebo ≥ 18 v Lenabasum 5 mg age ≥ 18
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.2926 ^[30]
Method	Poisson regression model
Parameter estimate	rate ratio
Point estimate	0.8568
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6425
upper limit	1.1426

Notes:

[29] - Estimated using a Poisson regression model with effects of treatment and log(subject treatment exposure duration) as offset and scale = deviance options, adjusting for FEV1 % predicted (<70 versus ≥ 70 predicted) at baseline, number of previous PEx requiring IV antibiotics in the previous year, baseline CFTR-targeting medications use (Yes, No), and region (United States versus Non-United States). P-values are for the comparison of lenabasum with placebo.

[30] - Lenabasum 5 mg vs placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of treatment period

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Lenabasum 20 mg
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Reporting group description:

Randomised treatment arm, in which patients were treated with the higher dose of lenabasum.

Reporting group title	Lenabasum 5 mg
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Reporting group description:

Randomised treatment arm, in which patients were treated with the lower dose of lenabasum.

Reporting group title	Placebo
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Reporting group description:

Randomised treatment arm, in which patients were treated with placebo.

Serious adverse events	Lenabasum 20 mg	Lenabasum 5 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 165 (30.30%)	25 / 89 (28.09%)	50 / 171 (29.24%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Pyrexia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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			
Testicular torsion			

subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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			
Cough			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Dyspnoea			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
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 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	3 / 165 (1.82%)	1 / 89 (1.12%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	42 / 165 (25.45%)	22 / 89 (24.72%)	41 / 171 (23.98%)
occurrences causally related to treatment / all	3 / 61	2 / 29	1 / 53
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 165 (0.00%)	1 / 89 (1.12%)	0 / 171 (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			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human rhinovirus test positive			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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 function test decreased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
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			
Injury			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Non-compaction cardiomyopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 165 (0.00%)	1 / 89 (1.12%)	0 / 171 (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 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	3 / 165 (1.82%)	1 / 89 (1.12%)	3 / 171 (1.75%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
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	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Calculus urinary			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
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 / 165 (0.00%)	1 / 89 (1.12%)	0 / 171 (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
Ureterolithiasis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 89 (1.12%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal disease carrier			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Influenza			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 89 (0.00%)	0 / 171 (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
Rhinovirus infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 89 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 165 (0.00%)	1 / 89 (1.12%)	0 / 171 (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	Lenabasum 20 mg	Lenabasum 5 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 165 (89.70%)	79 / 89 (88.76%)	148 / 171 (86.55%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	8 / 165 (4.85%)	6 / 89 (6.74%)	7 / 171 (4.09%)
occurrences (all)	9	7	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 165 (7.88%)	6 / 89 (6.74%)	6 / 171 (3.51%)
occurrences (all)	17	12	8
Headache			
subjects affected / exposed	24 / 165 (14.55%)	11 / 89 (12.36%)	16 / 171 (9.36%)
occurrences (all)	32	13	22
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 165 (12.73%)	10 / 89 (11.24%)	16 / 171 (9.36%)
occurrences (all)	25	11	16
Pyrexia			
subjects affected / exposed	16 / 165 (9.70%)	7 / 89 (7.87%)	12 / 171 (7.02%)
occurrences (all)	31	10	16
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 165 (6.06%)	5 / 89 (5.62%)	9 / 171 (5.26%)
occurrences (all)	11	6	10
Constipation			
subjects affected / exposed	10 / 165 (6.06%)	2 / 89 (2.25%)	5 / 171 (2.92%)
occurrences (all)	10	2	5
Diarrhoea			

subjects affected / exposed	10 / 165 (6.06%)	10 / 89 (11.24%)	10 / 171 (5.85%)
occurrences (all)	11	22	14
Nausea			
subjects affected / exposed	11 / 165 (6.67%)	6 / 89 (6.74%)	8 / 171 (4.68%)
occurrences (all)	13	7	11
Vomiting			
subjects affected / exposed	10 / 165 (6.06%)	3 / 89 (3.37%)	10 / 171 (5.85%)
occurrences (all)	11	4	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 165 (18.79%)	22 / 89 (24.72%)	29 / 171 (16.96%)
occurrences (all)	44	33	45
Dyspnoea			
subjects affected / exposed	8 / 165 (4.85%)	6 / 89 (6.74%)	8 / 171 (4.68%)
occurrences (all)	9	6	9
Haemoptysis			
subjects affected / exposed	19 / 165 (11.52%)	12 / 89 (13.48%)	17 / 171 (9.94%)
occurrences (all)	27	15	25
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	97 / 165 (58.79%)	50 / 89 (56.18%)	97 / 171 (56.73%)
occurrences (all)	196	93	180
Oropharyngeal pain			
subjects affected / exposed	5 / 165 (3.03%)	3 / 89 (3.37%)	9 / 171 (5.26%)
occurrences (all)	6	3	10
Rales			
subjects affected / exposed	11 / 165 (6.67%)	4 / 89 (4.49%)	12 / 171 (7.02%)
occurrences (all)	15	4	15
Sputum increased			
subjects affected / exposed	14 / 165 (8.48%)	11 / 89 (12.36%)	20 / 171 (11.70%)
occurrences (all)	19	17	25
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 165 (1.21%)	7 / 89 (7.87%)	3 / 171 (1.75%)
occurrences (all)	5	7	4
Nasopharyngitis			

subjects affected / exposed	18 / 165 (10.91%)	7 / 89 (7.87%)	16 / 171 (9.36%)
occurrences (all)	24	8	19
Sinusitis			
subjects affected / exposed	7 / 165 (4.24%)	10 / 89 (11.24%)	8 / 171 (4.68%)
occurrences (all)	9	11	8
Upper respiratory tract infection			
subjects affected / exposed	12 / 165 (7.27%)	5 / 89 (5.62%)	17 / 171 (9.94%)
occurrences (all)	13	6	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2017	<p>Reason for change: requested by FDA</p> <p>Key changes:</p> <p>Endpoints - Order of endpoints changed so that pulmonary exacerbation (PEx) rate was made primary endpoint (instead of secondary endpoint), and time to first exacerbation was demoted to a secondary endpoint. Moreover, for primary endpoint of PEx, the event had to meet 4/12 symptoms from Fuch's criteria, in presence of antibiotic usage for respiratory signs and symptoms.</p> <p>Sample size - Sample size changed from 315 randomized subjects to 415 randomized subjects, because of change in primary endpoint.</p> <p>Treatment discontinuation - Clarified that treatment discontinuation not the same as withdrawal from the study, and further details around data collection and reporting added for treatment discontinuations.</p> <p>Screening: clarified that rescreening was permitted.</p>
14 June 2018	<p>Reason for change: clarifications by sponsor; request of some health authorities</p> <p>Key changes:</p> <p>Potential risk - convulsions or seizures added. Subjects with a history of any seizure within the last 2 years were excluded to mitigate a potential risk of seizures identified in animal studies.</p> <p>Premature study termination or suspension: Modified study stop/suspension criteria from 2 life-threatening clinical events deemed probably/definitely related to study drug to 1 related event.</p> <p>Safety reporting - Added the Sponsor's responsibilities for reporting SUSARs per local country regulatory requirements.</p> <p>DMC - Clarified DMC responsibilities and members.</p>
09 October 2019	<p>Reason for change: clarifications and additional objective added by sponsor</p> <p>Key changes:</p> <p>Endpoints and objectives - Addition of a second tertiary efficacy objective and corresponding endpoints: To evaluate recovery from PEx in lenabasum 20 mg BID, lenabasum 5 mg BID, and placebo.</p> <p>Follow-up - Addition of language to indicate subjects would be asked to participate in a 2-year safety follow-up study. Subjects who agreed to participate in the follow-up study would be consented under a separate protocol.</p> <p>Primary endpoint - Clarification of Definition of Pulmonary Exacerbation: addition of phrase "Physician diagnosis of pulmonary exacerbation" to the primary definition.</p> <p>Responder definition - Addition of definition of Early Rapid Responder: Early rapid responders will be defined in several ways including but not limited to achieving a certain degree of improvement in FEV1, improvement in CRISS score, and improvement of other related measurements within a certain period of time.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported