EU Clinical Trials Register

Clinical trial results:
A Phase 3 Efficacy and Safety Study of PTC124 as an Oral Treatment for Nonsense-Mutation-Mediated Cystic Fibrosis

Summary

EudraCT number	2008-003924-52
Trial protocol	SE NL BE ES FR GB IT DE
Global end of trial date	12 November 2011

Results information

Result version number	v2 (current)
This version publication date	06 June 2020
First version publication date	03 May 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-009-CF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00803205
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	100 Corporate Court, South Plainfield, United States, NJ 07080
Public contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics International Limited, +353 1-906-8700, medinfo@ptcbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000115-PIP02-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 May 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2011
Global end of trial reached?	Yes
Global end of trial date	12 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of ataluren to improve pulmonary function as assessed by forced expiratory volume in 1 second (FEV1).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	238
EEA total number of subjects	119

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)	17
Adolescents (12-17 years)	58
Adults (18-64 years)	163
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 299 male and female participants with nonsense-mutation-mediated cystic fibrosis (nmCF) aged ≥6 years (y) signed the informed consent form and were screened for eligibility, of which 61 did not meet entry criteria to participate in the study.

Pre-assignment

Screening details:

A total of 238 participants were randomized in a 1:1 ratio to either ataluren or placebo. Six participants (4 in the ataluren arm; 2 in the placebo arm) were excluded from the Intent-to-Treat (ITT) population because they did not have at least 1 post-Baseline (BL) forced expiratory volume (FEV1) assessment by Week 8.

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ataluren As-Treated

Arm description:

Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	
Other name	PTC124, Translarna
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Ataluren was provided as a vanilla-flavored powder and was mixed with water. Participants received 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg).

Arm title	Placebo As-Treated

Arm description:

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching to ataluren was provided. Participants received 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg).

Number of subjects in period 1	Ataluren As-Treated	Placebo As-Treated
Started	120	118
Completed Week 16	107	113
Completed Week 24	103	110
As-Treated Population*	120	118
Intent-to-Treat (ITT) Population	116	116
Per Protocol Population	100	103 [1]
Completed	100	104
Not completed	20	14
Medical Monitor Decision	1	-
Consent withdrawn by subject	9	9
Physician decision	1	-
Acquired a Lung Infection	-	1
Adverse event, non-fatal	7	2
Sponsor Decision	-	1
Lost to follow-up	1	-
Protocol deviation	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant did not contribute data for FEV1 at Week 48.

Baseline characteristics

Reporting groups

Reporting group title	Ataluren As-Treated
Reporting group description:	

Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Reporting group title	Placebo As-Treated
Reporting group description:	

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Reporting group values	Ataluren As-Treated	Placebo As-Treated	Total
Number of subjects	120	118	238
Age, Customized			
Units: Subjects			
Participants aged 6 (min) to 53 (max) years old	120	118	238
Age Continuous			
Units: years			
arithmetic mean	23.0	23.2	
standard deviation	± 10.06	± 9.24	-
Sex: Female, Male			
Units: Subjects			
Female	58	59	117
Male	62	59	121

Subject analysis sets

Subject analysis set title	Ataluren ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	

Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.

Subject analysis set title	Placebo ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.

Reporting group values	Ataluren ITT	Placebo ITT	
Number of subjects	116	116	
Age, Customized			
Units: Subjects			
Participants aged 6 (min) to 53 (max) years old	116	116	

Age Continuous Units: years			
arithmetic mean	22.8	23.2	
standard deviation	± 10.18	± 9.32	
Sex: Female, Male Units: Subjects			
Female	56	58	
Male	60	58	

End points

End points reporting groups

Reporting group title	Ataluren As-Treated
Reporting group description:	
Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.	
Reporting group title	Placebo As-Treated
Reporting group description:	
Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.	
Subject analysis set title	Ataluren ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.	
Subject analysis set title	Placebo ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.	

Primary: Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in One Second (FEV1) at Baseline

End point title	Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in One Second (FEV1) at Baseline
End point description:	
Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FEV1 (the amount of air that can be exhaled in 1 second). Spirometry was assessed by using current guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). Baseline was the average of percent-predicted FEV1 at screening and randomization. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.	
End point type	Primary
End point timeframe:	
Baseline (Week 1)	

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: percentage of predicted FEV1				
arithmetic mean (standard deviation)	62.092 (± 13.6159)	60.232 (± 15.1437)		

Statistical analyses

Statistical analysis title	Ataluren, Placebo Baseline Analysis
Comparison groups	Ataluren ITT v Placebo ITT
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3264
Method	ANOVA

Primary: Percentage Change From Baseline in Percent-Predicted of FEV1 at Week 48

End point title	Percentage Change From Baseline in Percent-Predicted of FEV1 at Week 48

End point description:

Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FEV1 (the amount of air that can be exhaled in 1 second). Spirometry was assessed by using current guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). The percentage of change in percent-predicted of FEV1 was calculated as follows: ([percent-predicted FEV1-Baseline percent-predicted FEV1]/Baseline percent-predicted FEV1)*100. Baseline was the average of percent-predicted FEV1 at screening and randomization. A negative change from Baseline indicates that percent-predicted of FEV1 decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

End of Treatment (EOT) (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	103		
Units: percent change				
arithmetic mean (standard deviation)	-2.534 (± 13.2452)	-5.500 (± 12.5595)		

Statistical analyses

Statistical analysis title	Analysis of Percent-Predicted FEV1 At Week 48

Statistical analysis description:

Least squares (LS) mean estimates based on mixed model for repeated measures (Weeks 8, 16, 24, 32, 40 and 48) of relative change in percent-predicted FEV1 as the dependent variable; independent variables including Baseline percent-predicted FEV1, treatment, visit, interactions between treatment and visit and between Baseline percent-predicted FEV1 and visit; and stratification factors of Baseline age, Baseline inhaled antibiotics, and Baseline percent-predicted FEV1.

Comparison groups	Ataluren ITT v Placebo ITT

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1235 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.754
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.756
upper limit	6.264
Variability estimate	Standard error of the mean
Dispersion value	1.78124

Notes:

[1] - The p-value is the LS-mean for the comparison between active treatment and placebo. The level of significance was 0.04998.

Secondary: Rate of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria Over 48 Weeks

End point title	Rate of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria Over 48 Weeks

End point description:

A Respiratory Event Form, which collected data on various signs, symptoms, and effects for each event, was completed by the Investigator when informed by the participant of a respiratory event. Pulmonary exacerbations were assessed by using the modified Fuchs' criteria, which defines an exacerbation as a respiratory event requiring treatment with parenteral antibiotics for any 4 of the following 12 symptoms, with or without intravenous antibiotics: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature >38°C; anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10% or more from a previously recorded value; or radiographic changes indicative of pulmonary function. The 48-week exacerbation rate was determined by adding the weekly rates for each arm and dividing the sum by 48.

End point type	Secondary

End point timeframe:

Baseline to EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: exacerbations				
arithmetic mean (confidence interval 95%)	1.42 (1.05 to 1.79)	1.78 (1.38 to 2.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Awake Cough Hourly Rate at Week 48

End point title	Change From Baseline in Awake Cough Hourly Rate at Week 48

End point description:

The frequency of awake cough was measured using the LifeShirt, which incorporates motion-sensing transducers, electrodes, a microphone, and a 3-axis accelerometer into a lightweight vest. The rate was determined by dividing the total number of coughs by 24 (the number of hours of the observation period). Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that coughing decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: coughs/hour				
arithmetic mean (standard deviation)				
Baseline (n=115, 114)	28.218 (± 20.2726)	24.472 (± 16.7828)		
Change From Baseline (n=97, 100)	-0.595 (± 18.3221)	0.882 (± 14.3936)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Respiratory Domain Score of the Revised Cystic Fibrosis Questionnaire (CFQ-R) at Week 48

End point title	Change From Baseline in the Respiratory Domain Score of the Revised Cystic Fibrosis Questionnaire (CFQ-R) at Week 48

End point description:

The CFQ-R consists of 44 items, including generic scales of physical functioning, role functioning, vitality, health perceptions, emotional functioning, and social functioning, and CF-specific scales of respiratory and digestive symptoms, body image, eating disturbances, and treatment burden. Each domain score ranges from 1 to 4. Scores were linearly transformed to a 0 to 100 scale, with higher scores indicating better health. Domain scores were calculated by using the following formula: 100 * (sum of responses - minimum possible sum)/ (maximum possible sum - minimum possible sum). The minimum possible sum = number of questions * 1; the maximum possible = the number of questions * 4. Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that health has worsened. Participants may have switched age groups during the study. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: units on a scale				
arithmetic mean (standard deviation)				
Aged 6-13 years, Baseline (n=18, 13)	77.78 (± 11.070)	79.49 (± 16.879)		
Aged 6-13 years, Change From Baseline (n=12, 7)	-0.69 (± 12.028)	-3.57 (± 21.973)		
Age ≥14 years, Baseline (n=95, 101)	70.06 (± 15.678)	65.95 (± 16.771)		
Age ≥14 years, Change From Baseline (n=81, 92)	-2.81 (± 18.365)	-3.32 (± 16.245)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent-Predicted of Forced Vital Capacity (FVC) at Baseline

End point title	Percent-Predicted of Forced Vital Capacity (FVC) at Baseline

End point description:

Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FVC (the amount of air that can be exhaled after taking a deep breath). Spirometry was assessed by using current guidelines of the ATS and ERS. Baseline was the average of percent-predicted FVC at screening and randomization. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 1)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: percentage of predicted FVC				
arithmetic mean (standard deviation)	78.332 (± 13.1825)	76.609 (± 13.3711)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Percent-Predicted of FVC at Week 48

End point title	Percentage Change From Baseline in Percent-Predicted of FVC at Week 48

End point description:

Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FVC (the amount of air that can be exhaled after taking a deep breath). Spirometry was assessed by using current guidelines of the ATS and ERS. The percentage of change in percent-predicted of FVC was calculated as follows: ((percent-predicted FVC-Baseline percent-predicted FVC)/Baseline percent-predicted FVC)*100. Baseline was the average of percent-predicted FVC at screening and randomization. A negative change from Baseline indicates that percent-predicted of FVC decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	103		
Units: percent change				
arithmetic mean (standard deviation)	-2.139 (± 10.0463)	-3.484 (± 9.9304)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With Treatment-Emergent Adverse Events (TEAE)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAE)

End point description:

A TEAE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship that occurred or worsened in the period extending from first dose of study drug to 4 weeks after the last dose of study drug. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. AE severity was graded as follows: Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal. A TEAE was considered related if in the opinion of the Investigator it was possibly or probably caused by the study drug. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the Adverse Events module.

End point type	Other pre-specified

End point timeframe:

Baseline up to 4 Weeks Post-Treatment (Week 52) or Premature Discontinuation (PD)

End point values	Ataluren As-Treated	Placebo As-Treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: percent of participants				
number (not applicable)				
At least 1 TEAE	98.3	97.5		
Grade 1 TEAE	15.0	16.9		
Grade 2 TEAE	67.5	55.1		
Grade 3 TEAE	15.8	25.4		
Grade 4 TEAE	0	0		
Grade 5 TEAE	0	0		
Unrelated TEAE	25.0	35.6		
Unlikely related TEAE	32.5	26.3		
Possibly related TEAE	28.3	29.7		
Probably related TEAE	12.5	5.9		
Discontinuation due to TEAE	6.7	2.5		
Serious TEAE	37.5	40.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Study Drug Compliance by Drug Accountability

End point title	Rate of Study Drug Compliance by Drug Accountability

End point description:

Study drug compliance was assessed by using a Pharmacy Subject Study Drug Accountability Log (completed by the investigational site personnel). The rate of compliance was defined as 100 * (number of sachets taken/number of planned sachets) during the study. All calculations were based on the records of the first dose date to the last dose date. To differentiate dose strengths while maintaining the blind, each kit had a unique kit number and had prominent lettering "A" and "B." Each kit contained 65 packets of 1 of the dose strengths (125, 250, or 1000 mg or matching placebo). Labeling for active drug and placebo was identical.

End point type	Other pre-specified

End point timeframe:

Baseline up to EOT (Week 48)

End point values	Ataluren As-Treated	Placebo As-Treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: percent of doses taken				
median (full range (min-max))				
Drug Kit A	90.149 (18.24 to 109.24)	85.119 (28.36 to 125.79)		
Drug Kit B	90.830 (13.27 to 116.67)	86.614 (25.22 to 107.60)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Study Drug Compliance by Patient-Reported Data

End point title	Rate of Study Drug Compliance by Patient-Reported Data

End point description:

Patient-reported data were obtained from the participant's electronic daily diary, which was completed by the participant or the caregiver. During study treatment, the electronic daily diary was to be completed by the participant or caregiver each day for each dose. For each participant, compliance is described in terms of the percentage of study drug actually taken. All calculations were based on the records of the first dose date to the last dose date. To differentiate dose strengths while maintaining the blind, each kit had a unique kit number and had prominent lettering "A" and "B." Each kit contained 65 packets of 1 of the dose strengths (125, 250, or 1000 mg or matching placebo). Labeling for active drug and placebo was identical.

End point type	Other pre-specified

End point timeframe:

Baseline up to EOT (Week 48)

End point values	Ataluren As-Treated	Placebo As-Treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: percent of doses taken				
median (full range (min-max))	71.48 (0 to 98.5)	69.27 (6.4 to 98.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concentration of Ataluren

End point title	Concentration of Ataluren[2]

End point description:

Blood samples were drawn immediately before administration of the first daily dose (dose taken with breakfast) of study drug and 2 hours after the first daily dose. Whenever possible, the pre-dose sample was to be obtained within 15 minutes of drug administration. Participants in the Placebo arm did not receive Ataluren and are not included in this End Point. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Predose and 2 Hours Postdose at Week 1, Week 16, Week 32, EOT (Week 48)

Notes:

[2] - 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: Participants in the Placebo arm did not receive Ataluren and are not included in this End Point.

End point values	Ataluren As-Treated			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: micrograms/milliliter (ug/mL)				
median (full range (min-max))				
Week 1 Predose (n=119)	0 (0 to 0)			
Week 1 Postdose (n=117)	14.100 (1.42 to 56.40)			
Week 16 Predose (n=103)	4.350 (0 to 52.60)			
Week 16 Postdose (n=104)	11.900 (0.80 to 41.90)			
Week 32 Predose (n=99)	4.630 (0 to 29.20)			
Week 32 Postdose (n=97)	13.400 (2.37 to 36.30)			
Week 48 Predose (n= 97)	3.970 (0 to 27.00)			
Week 48 Postdose (n=96)	10.500 (0 to 39.10)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Interventions for Respiratory Symptoms

End point title	Rate of Interventions for Respiratory Symptoms
End point description:	

During treatment, any intervention including hospitalization or use of oral, inhaled, or intravenous antibiotics was documented if it was due to an exacerbation-like episode. Participants and caregivers recorded interventions in an electronic diary. The rate of interventions was defined as the total days with interventions divided by the total study duration.

End point type	Other pre-specified
End point timeframe:	

Baseline up to EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: days with interventions during the study				
arithmetic mean (standard deviation)				
Hospitalization	0.010 (± 0.0222)	0.021 (± 0.0469)		

Use of Antibiotics	0.220 (± 0.2284)	0.245 (± 0.2380)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms

End point title	Rate of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms
End point description:	

During treatment, any disruption in the activities of daily living, such as missed school or work, was documented if it was due to an exacerbation-like episode. Participants and caregivers recorded all disruptions in an electronic diary. The rate of disruptions was defined as the total days with disruptions to daily living divided by the total study duration.

End point type	Other pre-specified
End point timeframe:	

Baseline up to EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: days with disruption during the study				
arithmetic mean (standard deviation)	0.037 (± 0.0550)	0.047 (± 0.0755)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Body Weight at Week 48

End point title	Change From Baseline in Body Weight at Week 48
End point description:	

Participants were weighed, and the weight was recorded at Baseline and then every 8 weeks during the treatment period. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that weight increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified
End point timeframe:	

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=116, 116)	53.46 (± 13.941)	56.01 (± 13.149)		
Change From Baseline (n=100, 104)	0.87 (± 3.342)	0.83 (± 3.101)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in the Concentration of Interleukin-8 (IL-8) in Serum and Sputum at Week 48

End point title	Change From Baseline in the Concentration of Interleukin-8 (IL-8) in Serum and Sputum at Week 48

End point description:

Expression of IL-8 was measured in serum and in sputum. Sputum was spontaneously produced and tested by using standardized procedures developed by the Cystic Fibrosis Foundation Therapeutics, Inc. Therapeutics Development Network (CFFT-TDN). Baseline was the latest valid assessment prior to the treatment. A negative change from Baseline indicates that the concentration of IL-8 decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: picograms/mL				
arithmetic mean (standard deviation)				
Serum, Baseline (n=115, 116)	39.537 (± 14.1697)	55.845 (± 131.8505)		
Serum, Change From Baseline (n=96, 103)	-2.334 (± 13.2141)	-16.197 (± 138.3108)		
Sputum, Baseline (n=94, 95)	267629.93 (± 259089.569)	250170.95 (± 180581.976)		
Sputum, Change From Baseline (n=73, 81)	28882.79 (± 199160.845)	9957.24 (± 166348.660)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in the Concentration of Neutrophil Elastase in Sputum at Week 48

End point title	Change From Baseline in the Concentration of Neutrophil Elastase in Sputum at Week 48
End point description:	
Expression of neutrophil elastase was measured in sputum. Sputum was spontaneously produced and tested by using standardized procedures developed by the CFFT-TDN. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that the concentration of neutrophil elastase increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.	
End point type	Other pre-specified
End point timeframe:	
Baseline, EOT (Week 48)	

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[3]	94[4]		
Units: ug/mL				
arithmetic mean (standard deviation)				
Baseline (n=94, 94)	183.64 (± 221.901)	227.35 (± 227.881)		
Change From Baseline (n=73, 80)	5.45 (± 232.824)	-8.67 (± 296.105)		

Notes:

[3] - Twenty-two participants in the ataluren group were not evaluable.

[4] - Twenty-two participants in the placebo group were not evaluable.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in the Concentration of C-Reactive Protein (CRP) in Serum at Week 48

End point title	Change From Baseline in the Concentration of C-Reactive Protein (CRP) in Serum at Week 48
End point description:	
Expression of CRP was measured in serum. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that CRP concentration increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.	
End point type	Other pre-specified
End point timeframe:	
Baseline, EOT (Week 48)	

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: mg/liter (L)				
arithmetic mean (standard deviation)				
Baseline (n=115, 116)	6.899 (± 11.5869)	7.037 (± 8.4411)		
Change From Baseline (n=96, 103)	2.420 (± 10.5162)	2.031 (± 10.1202)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in the Total Lung Score as Assessed by Computed Tomography (CT) at Week 48

End point title	Change From Baseline in the Total Lung Score as Assessed by Computed Tomography (CT) at Week 48

End point description:

Lungs were imaged by using non-contrast, spiral CT. The total lung score for each CT scan was established by the sum of 5 characteristics from the Brody scoring system, with scores ranging from 0 to 40.5, with lower scores indicating better lung function. The characteristics scored were bronchiectasis (score range 0 – 12), mucus plugging (score range 0 – 6), peribronchial thickening (score range 0 – 9), parenchyma (score range 0 – 9), and hyperinflation (score range 0 – 4.5). Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that lung function worsened. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105[5]	106[6]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=105, 106)	9.531 (± 3.7526)	9.619 (± 3.4244)		
Change From Baseline (n=99, 104)	0.282 (± 1.3441)	0.560 (± 1.5602)		

Notes:

[5] - Eleven participants in the ataluren group were not evaluable.

[6] - Ten participants in the placebo group were not evaluable.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Total Nasal Chloride Transport as Assessed by Transepithelial Potential Difference (TEPD) at Week 48

End point title	Change From Baseline in Total Nasal Chloride Transport as

	Assessed by Transepithelial Potential Difference (TEPD) at Week 48

End point description:

TEPD was assessed in each nostril using standardized equipment, techniques, and solutions. Assessments were made on the nasal epithelium cells lining the inferior turbinate. Warmed solutions of Ringer's solution, amiloride, chloride-free gluconate, isoproterenol, and adenosine triphosphate (ATP) were perfused for ≥3-minute sequentially through a nasal catheter while a voltage tracing was recorded. Total chloride transport was computed for each nostril. The total chloride transport values were calculated by subtracting the voltages at the end of a perfusion from the voltage at the end of an earlier perfusion (isoproterenol-amiloride). The average of the values for each nostril was computed. If the assessment was available in only 1 nostril, this value was used as if it were the average of both nostrils. A positive change from Baseline indicates that nasal chloride transport increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	116		
Units: millivolts				
arithmetic mean (standard deviation)				
Baseline (n=116, 116)	1.578 (± 3.8786)	1.950 (± 3.5462)		
Change From Baseline (n=100, 104)	0.312 (± 5.0574)	0.139 (± 5.8139)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Sweat Chloride Concentration at Week 48

End point title	Change From Baseline in Sweat Chloride Concentration at Week 48

End point description:

Sweat was collected, from each arm, by using pilocarpine iontophoresis. The chloride concentration in the sweat was quantified for each arm by using standard laboratory methods. Tests were also considered valid if the sweat collection time was ≤35 minutes; tests with longer collection times were also considered valid if extra time was needed to obtain sufficient volume (≥15uL) for analysis. For analysis purposes, the average of the values from each arm were computed. If the assessment was valid and/or available in only 1 arm, this value was used as if it were the average of both arms. The method used was consistent with the CFFT-TDN guidelines. Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that sweat chloride concentration decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Baseline, EOT (Week 48)

End point values	Ataluren ITT	Placebo ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114[7]	111[8]		
Units: millimoles/L				
arithmetic mean (standard deviation)				
Baseline (n=114, 111)	100.140 (± 14.2170)	96.586 (± 15.9279)		
Change From Baseline (n=97, 97)	-1.325 (± 8.9431)	-0.619 (± 10.2657)		

Notes:

[7] - Two participants in the ataluren group were not evaluable.

[8] - Five participants in the placebo group were not evaluable.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 4 Weeks Post-Treatment (Week 52) or Premature Discontinuation (PD)

Adverse event reporting additional description:

The As-Treated Population: all randomized participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Reporting group title	Ataluren

Reporting group description:

Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

Serious adverse events	Placebo	Ataluren	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 118 (42.37%)	46 / 120 (38.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Drug withdrawal syndrome		
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Immune system disorders		
Drug hypersensitivity		
subjects affected / exposed	1 / 118 (0.85%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders		
Cystic fibrosis long		
subjects affected / exposed	41 / 118 (34.75%)	34 / 120 (28.33%)
occurrences causally related to treatment / all	0 / 66	0 / 47
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoptysis		
subjects affected / exposed	3 / 118 (2.54%)	2 / 120 (1.67%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Nasal polyps		
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders		
Depression		
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Injury, poisoning and procedural complications		
Post procedural haemorrhage		

subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 118 (0.85%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Biliary colic				
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholelithiasis				
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	0 / 118 (0.00%)	3 / 120 (2.50%)		
occurrences causally related to treatment / all	0 / 0	2 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal failure acute				
subjects affected / exposed	0 / 118 (0.00%)	3 / 120 (2.50%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal colic				
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary retention				
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Musculoskeletal and connective tissue disorders				
Hypercreatinaemia				
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infections and infestations				
Pneumonia				

subjects affected / exposed	0 / 118 (0.00%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 118 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterium abscessus infection			
subjects affected / exposed	2 / 118 (1.69%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 118 (0.85%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ataluren	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 118 (97.46%)	118 / 120 (98.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 118 (11.86%)	20 / 120 (16.67%)	
occurrences (all)	34	38	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 118 (18.64%)	17 / 120 (14.17%)	
occurrences (all)	30	28	
Fatigue			
subjects affected / exposed	11 / 118 (9.32%)	11 / 120 (9.17%)	
occurrences (all)	12	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 118 (11.86%)	20 / 120 (16.67%)	
occurrences (all)	20	38	
Vomiting			
subjects affected / exposed	11 / 118 (9.32%)	14 / 120 (11.67%)	
occurrences (all)	13	16	
Diarrhoea			
subjects affected / exposed	21 / 118 (17.80%)	13 / 120 (10.83%)	
occurrences (all)	27	18	
Abdominal pain upper			

subjects affected / exposed	7 / 118 (5.93%)	11 / 120 (9.17%)	
occurrences (all)	22	15	
Nausea			
subjects affected / exposed	13 / 118 (11.02%)	11 / 120 (9.17%)	
occurrences (all)	19	13	
Constipation			
subjects affected / exposed	9 / 118 (7.63%)	7 / 120 (5.83%)	
occurrences (all)	10	9	
Respiratory, thoracic and mediastinal disorders			
Cystic fibrosis lung			
subjects affected / exposed	82 / 118 (69.49%)	85 / 120 (70.83%)	
occurrences (all)	190	168	
Cough			
subjects affected / exposed	35 / 118 (29.66%)	28 / 120 (23.33%)	
occurrences (all)	70	47	
Productive cough			
subjects affected / exposed	11 / 118 (9.32%)	12 / 120 (10.00%)	
occurrences (all)	14	16	
Haemoptysis			
subjects affected / exposed	16 / 118 (13.56%)	9 / 120 (7.50%)	
occurrences (all)	25	18	
Rales			
subjects affected / exposed	6 / 118 (5.08%)	6 / 120 (5.00%)	
occurrences (all)	7	8	
Respiratory tract congestion			
subjects affected / exposed	8 / 118 (6.78%)	5 / 120 (4.17%)	
occurrences (all)	10	6	
Oropharyngeal pain			
subjects affected / exposed	14 / 118 (11.86%)	4 / 120 (3.33%)	
occurrences (all)	20	5	
Bronchospasm			
subjects affected / exposed	6 / 118 (5.08%)	1 / 120 (0.83%)	
occurrences (all)	6	1	
Renal and urinary disorders			

Nephrolithiasis		
subjects affected / exposed	4 / 118 (3.39%)	8 / 120 (6.67%)
occurrences (all)	4	9
Dysuria		
subjects affected / exposed	1 / 118 (0.85%)	7 / 120 (5.83%)
occurrences (all)	1	8
Musculoskeletal and connective tissue disorders		
Back pain		
subjects affected / exposed	6 / 118 (5.08%)	8 / 120 (6.67%)
occurrences (all)	6	8
Hypercreatinaemia		
subjects affected / exposed	1 / 118 (0.85%)	8 / 120 (6.67%)
occurrences (all)	1	13
Infections and infestations		
Viral upper respiratory tract infection		
subjects affected / exposed	32 / 118 (27.12%)	21 / 120 (17.50%)
occurrences (all)	37	27
Sinusitis		
subjects affected / exposed	14 / 118 (11.86%)	15 / 120 (12.50%)
occurrences (all)	25	18
Rhinitis		
subjects affected / exposed	13 / 118 (11.02%)	12 / 120 (10.00%)
occurrences (all)	16	13
Nasopharyngitis		
subjects affected / exposed	8 / 118 (6.78%)	10 / 120 (8.33%)
occurrences (all)	12	15
Pharyngitis		
subjects affected / exposed	4 / 118 (3.39%)	7 / 120 (5.83%)
occurrences (all)	4	7
Upper respiratory tract infection		
subjects affected / exposed	12 / 118 (10.17%)	5 / 120 (4.17%)
occurrences (all)	16	6
Metabolism and nutrition disorders		
Abnormal loss of weight		
subjects affected / exposed	5 / 118 (4.24%)	10 / 120 (8.33%)
occurrences (all)	5	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2010	This amendment introduced the following changes: * Updates of results of Phase 1 and Phase 2 clinical studies in the cystic fibrosis and Duchene/Becker muscular dystrophy populations. * Addition of endpoints related to the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire. * Updates of eligibility criteria, frequency of laboratory assessment, treatment with concomitant medications, blood collection, and adverse events reporting. * Updates of procedures for subject enrollment. * Update to plans for statistical analyses and interim analyses, blinding, and unblinding. * Inclusion of summary of findings related to renal dysfunction in this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

 http://www.ncbi.nlm.nih.gov/pubmed/24836205