Clinical trial results:
An Open-Label Safety and Efficacy Study for Patients With Nonsense Mutation Cystic Fibrosis Previously Treated With Ataluren (PTC 124)

Summary

EudraCT number	2013-005449-35
Trial protocol	BE SE IT DE ES FR
Global end of trial date	05 June 2017

Results information

Result version number	v1 (current)
This version publication date	27 March 2020
First version publication date	27 March 2020

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-023-CF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02107859
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 19068700, medinfo@ptcbio.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2017
Global end of trial reached?	Yes
Global end of trial date	05 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the long-term safety and tolerability of 10, 10, 20 milligrams/ kilogram (mg/kg) ataluren in participants with nonsense mutation cystic fibrosis (nmCF) who completed participation in the double-blind study PTC124-GD-009-CF (NCT00803205) as assessed by adverse events and laboratory abnormalities.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000) and in conformance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2014
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: 20
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	61
EEA total number of subjects	24

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	0

months)	
Children (2-11 years)	2
Adolescents (12-17 years)	7
Adults (18-64 years)	52
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with nmCF who had completed the double-blind study PTC124-GD-009-CF (NCT00803205) were enrolled and treated in this open-label extension study.

Pre-assignment

Screening details:

On 2 March 2017, it was announced that the Phase 3 double-blind study PTC124-GD-021-CF (NCT02139306) did not achieve its primary or secondary endpoints. Based on these results, clinical development of ataluren in cystic fibrosis was discontinued and this ongoing open-label extension study was closed.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ataluren

Arm description:

Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	PTC124
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Ataluren will be administered per dose and schedule specified in the arm.

Number of subjects in period 1	Ataluren
Started	61
As-treated population	61
Intent-to-treat (ITT) population	60
Completed	0
Not completed	61
Consent withdrawn by subject	14
Adverse event, non-fatal	3
Other than specified	3
Study closure	41

Baseline characteristics

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.	

Reporting group values	Ataluren	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
Children (2-11 years)	2	2	
Adolescents (12-17 years)	7	7	
Adults (18-64 years)	52	52	
Age Continuous Units: years			
arithmetic mean	27.5		
standard deviation	± 10.73	-	
Sex: Female, Male Units: participants			
Female	34	34	
Male	27	27	
Race/Ethnicity, Customized Units: Subjects			
White-White/Caucasian	61	61	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	60	60	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Ataluren

Reporting group description:

Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

AE: any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severity of an AE was classified as: mild (does not interfere with usual function), moderate (interferes to some extent with usual function), severe (interferes significantly with usual function), life threatening, and fatal AEs. Drug-related AEs: AEs with a possible or probable relationship to study drug. Serious AEs: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event required medical intervention. TEAE: AE that occurred or worsened from first dose of study drug to 4 weeks after last dose. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. As-treated population: all participants who received at least 1 dose of ataluren.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to end of study (Week 196)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety analyses were descriptive in nature.

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: participants				
Any TEAEs	61			
Mild AEs	4			
Moderate AEs	26			
Severe AEs	30			
Life-threatening AEs	0			
Fatal AEs	1			
AEs unrelated to ataluren	35			
AEs unlikely related to ataluren	12			
AEs possible related to ataluren	13			
AEs probable related to ataluren	1			
Serious TEAEs	36			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Laboratory Abnormalities

End point title	Number of Participants With Clinically Significant Laboratory Abnormalities[2]

End point description:

Laboratory parameters tests included hematology, biochemistry assay (hepatic, renal, and serum electrolyte values), adrenal assays, and urinalysis. Clinical significance was defined as per investigator's judgement. As-treated population included all participants who received at least 1 dose of ataluren.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to end of study (Week 196)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety analyses were descriptive in nature.

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at the End of Treatment (Week 192), as Assessed by Spirometry

End point title	Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at the End of Treatment (Week 192), as Assessed by Spirometry

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Percent of predicted FEV1 = (observed value)/(predicted value) * 100%. Change from baseline in percent predicted FEV1 at the end of treatment was reported. ITT population included all participants who had at least 1 post-baseline efficacy assessment. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: percentage of predicted FEV1				
arithmetic mean (standard deviation)				
Baseline (n = 59)	56.203 (± 17.2964)			

Change at Week 192 (n = 7)	-1.214 (± 3.6384)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Modified Fuchs Criteria

End point title	Percentage of Participants With Pulmonary Exacerbation, As Assessed by Modified Fuchs Criteria

End point description:

The modified Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms without the requirement for treatment with antibiotics: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature greater than (>) 38 degrees celsius (°C); anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (not applicable)	68.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Expanded Fuchs' Criteria

End point title	Percentage of Participants With Pulmonary Exacerbation, As Assessed by Expanded Fuchs' Criteria

End point description:

The expanded Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms requiring any form of antibiotic treatment (inhaled, oral, or intravenous): 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 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (not applicable)	68.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Classic Fuchs' Criteria

End point title	Percentage of Participants With Pulmonary Exacerbation, As Assessed by Classic Fuchs' Criteria

End point description:

The Classic Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms requiring treatment with parenteral 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 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (not applicable)	58.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 12-Lead Electrocardiogram (ECG) Parameters at Final Visit (Week 196)

End point title	Change From Baseline in 12-Lead Electrocardiogram (ECG) Parameters at Final Visit (Week 196)

End point description:

ECG parameters included RR duration, PR duration, QRS duration, QT duration, QTCB (Bazett's correction formula) duration, QTCF (Fridericia's correction formula) duration. As-treated population included all participants who received at least 1 dose of ataluren. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 196

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: miiliseconds				
arithmetic mean (standard deviation)				
Baseline: RR duration (n=59)	828.17 (± 132.15)			
Change at Week 196: RR duration (n=55)	-14.27 (± 115.62)			
Baseline: PR duration (n=59)	145.02 (± 19.29)			
Change at Week 196: PR duration (n=55)	-2.69 (± 12.25)			
Baseline: QRS duration (n=59)	83.90 (± 8.00)			
Change at Week 196: QRS duration (n=55)	0.33 (± 6.12)			
Baseline: QT duration (n=59)	370.71 (± 28.11)			
Change at Week 196: QT duration (n=55)	-4.38 (± 25.63)			
Baseline: QTCB duration (n=59)	408.92 (± 22.05)			
Change at Week 196: QTCB duration (n=55)	-0.71 (± 17.96)			
Baseline: QTCF duration (n=59)	395.47 (± 19.23)			
Change at Week 196: QTCF duration (n=59)	-2.27 (± 17.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Heart Rate at Final Visit (Week 196), as Assessed by 12-Lead ECG

End point title	Change From Baseline in Heart Rate at Final Visit (Week 196), as Assessed by 12-Lead ECG

End point description:

Heart rate was measured using 12-lead ECG. As-treated population included all participants who received at least 1 dose of ataluren. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:
Baseline, Week 196

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: beats/minute				
arithmetic mean (standard deviation)				
Baseline (n = 59)	74.31 (± 12.06)			
Change at Week 196 (n = 55)	2.04 (± 10.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs at Final Visit (Week 196)

End point title	Change From Baseline in Vital Signs at Final Visit (Week 196)

End point description:

Vital Signs included systolic blood pressure (SBP), diastolic blood pressure (DBP). As-treated population included all participants who received at least 1 dose of ataluren. Here, 'n' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:
Baseline, Week 196

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline: SBP (n=61)	114.8 (± 9.10)			
Change at Week 196: SBP (n=59)	0.6 (± 12.62)			
Baseline: DBP (n=61)	71.2 (± 8.93)			
Change at Week 196: DBP (n=59)	-0.3 (± 9.93)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Percent Predicted Forced Vital

Capacity (FVC) at the End of Treatment (Week 192), as Assessed by Spirometry

End point title	Change From Baseline in Percent Predicted Forced Vital Capacity (FVC) at the End of Treatment (Week 192), as Assessed by Spirometry

End point description:

FVC is the volume of air that can forcibly be blown out after full inspiration in the upright position. Percent of predicted FVC = (observed value)/(predicted value) * 100%. Change from baseline in percent predicted FVC at the end of treatment was reported. ITT population included all participants who had at least 1 post-baseline efficacy assessment. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable at specified timepoint.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: percentage of predicted FVC				
arithmetic mean (standard deviation)				
Baseline (n = 59)	73.576 (± 14.6552)			
Change at Week 192 (n = 7)	-2.286 (± 4.5722)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Percent Predicted Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at the End of Treatment (Week 192), as Assessed by Spirometry

End point title	Change From Baseline in Percent Predicted Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at the End of Treatment (Week 192), as Assessed by Spirometry

End point description:

FEF25-75 is the forced expiratory flow between 25 and 75% of vital capacity.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 192

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: percent predicted FEV1				
arithmetic mean (standard deviation)	()			

Notes:

[3] - Due to change in planned analysis FEV25-75 was not calculated and summarized.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (Week 196)

Adverse event reporting additional description:

As-treated population included all participants who received at least 1 dose of ataluren.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Ataluren

Reporting group description:

Participants received ataluren suspension orally TID, 10 mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

Serious adverse events	Ataluren		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 61 (59.02%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Forced expiratory volume decreased			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test decreased			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Distal ileal obstruction syndrome			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Distal intestinal obstruction syndrome			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Gallbladder pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Device related infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	27 / 61 (44.26%)		
occurrences causally related to treatment / all	1 / 70		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ataluren		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 12		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	 5 / 61 (8.20%) 5		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 6 / 61 (9.84%) 6 5 / 61 (8.20%) 8 7 / 61 (11.48%) 9 8 / 61 (13.11%) 8 4 / 61 (6.56%) 4 6 / 61 (9.84%) 7 4 / 61 (6.56%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all)	 9 / 61 (14.75%) 39 12 / 61 (19.67%) 22		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 6		
Back pain subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 6		
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	50 / 61 (81.97%) 147		
Influenza subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 9		
Oral candidiasis subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 5		
Sinusitis subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 6		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 19		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	22 / 61 (36.07%) 34		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2015	It included following changes: • Treatment duration as changed from 48 to 96 weeks to allow participants prolonged access to study drug and possibility of weight-based dose adjustment at Week 64 was added. • The approximate number of enrolled participants was changed from 80 to 70. • An inclusion criterion was clarified to reflect that all screening laboratory results were to be received, reviewed, and deemed acceptable for study participation prior to enrollment. • The assessment of adrenocorticotropic hormone (ACTH), found to be obsolete and for which no relevant change had been found, was removed. • A table of required laboratory values at screening was deleted and the inclusion criterion revised to reflect that values were to be within the central laboratory reference range. • Exclusion criteria were modified to clarify exclusion for chronic use of inhaled or systemic tobramycin within 4 weeks prior to screening and for evidence of pulmonary exacerbation between screening and enrollment. • Serum electrolyte parameters were removed from the table of safety monitoring laboratory parameters to allow participants to continue in study at the investigator's discretion. • The Schedule of Events was updated to clarify visit windows. • Long-term follow-up period was removed based upon lack of safety issues identified in previous studies. • Total bilirubin was added to the list of serum biochemistry assessments. • Concomitant medication information collection was clarified. • Sputum data collection requirements were clarified. • Instructions to withhold short-acting beta agonists (SABAs) and long-acting beta agonists (LABAs) prior to spirometry testing were added. • Clarification was provided for reporting of pulmonary exacerbations and pregnancy outcomes as serious adverse events (SAEs). • Text was updated to reflect electronic data capture (EDC) as the primary method for SAE reporting for sites.
08 February 2016	It included following changes: • Treatment duration as changed from 96 to 192 weeks to allow participants extended access to study drug, and additional weight-based dose adjustment timepoints were added. Text was updated throughout the protocol to reflect the new duration. • Respiratory event evaluation was added to Phone Visit 5a. • Five-year long-term follow-up assessment for non-CF AEs was removed. • Contact information was updated to reflect change in the contract research organization (CRO). • Minor text editorial and administrative changes were made for consistency and accuracy throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Based on the results of study PTC124-GD-021-CF (NCT02139306) (did not achieve its primary or secondary endpoints), clinical development of ataluren in cystic fibrosis was discontinued and this ongoing open-label extension study was closed.

Notes: