



## Clinical trial results: A Phase 3 Efficacy and Safety Study of Ataluren (PTC124®) in Patients with Nonsense Mutation Cystic Fibrosis

### Summary

EudraCT number	2013-004581-34
Trial protocol	IT BE DE NL ES GB BG GR
Global end of trial date	02 November 2016

### Results information

Result version number	v1 (current)
This version publication date	17 April 2020
First version publication date	17 April 2020

### Trial information

#### Trial identification

Sponsor protocol code	PTC124-GD-021-CF
-----------------------	------------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02139306
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	100 Corporate Court, South Plainfield, United States, 07080
Public contact	Medical Information, PTC Therapeutics, Inc., +353 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)	Yes
EMA paediatric investigation plan number(s)	EMA-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	25 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2016
Global end of trial reached?	Yes
Global end of trial date	02 November 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the ability of ataluren to improve pulmonary function relative to placebo by analysing the absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) at Week 48, defined as the average between the change at Week 40 and that at Week 48.

Protection of trial subjects:

The trial was conducted in accordance with 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	15 August 2014
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	Australia: 16
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 85

Worldwide total number of subjects	279
EEA total number of subjects	147

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)	44
Adolescents (12-17 years)	71
Adults (18-64 years)	164
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted from 15 August 2014 to 02 November 2016.

### Pre-assignment

Screening details:

A total of 449 participants were enrolled, of which 170 did not qualify for the study due to failure to meet entry criteria. A total of 279 participants were randomized and received study drugs.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ataluren

Arm description:

Participants received ataluren as oral powder for suspension at the dosages of 10, 10, and 20 milligrams/kilograms (mg/kg) at morning, midday, and evening, respectively for 48 weeks of treatment duration or until treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	Ataluren (PTC124®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Ataluren was administered as per the dose and schedule specified in the respective arms.

<b>Arm title</b>	Placebo
------------------	---------

Arm description:

Participants received matching placebo orally at morning, midday, and evening for 48 weeks of treatment duration or until treatment discontinuation.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to ataluren was administered as per the dose and schedule specified in the respective arms.

<b>Number of subjects in period 1</b>	Ataluren	Placebo
Started	140	139
Completed	127	125
Not completed	13	14
Consent withdrawn by subject	4	6
Physician decision	-	1
Adverse event, non-fatal	3	4
Protocol deviation	4	-
Other Unspecified	2	3

## Baseline characteristics

### Reporting groups

Reporting group title	Ataluren
-----------------------	----------

Reporting group description:

Participants received ataluren as oral powder for suspension at the dosages of 10, 10, and 20 milligrams/kilograms (mg/kg) at morning, midday, and evening, respectively for 48 weeks of treatment duration or until treatment discontinuation.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received matching placebo orally at morning, midday, and evening for 48 weeks of treatment duration or until treatment discontinuation.

Reporting group values	Ataluren	Placebo	Total
Number of subjects	140	139	279
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	25	19	44
Adolescents (12-17 years)	34	37	71
Adults (18-64 years)	81	83	164
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	22.0	22.0	
standard deviation	± 11.00	± 10.44	-
Gender Categorical			
Units: Subjects			
Female	59	74	133
Male	81	65	146

## End points

### End points reporting groups

Reporting group title	Ataluren
Reporting group description: Participants received ataluren as oral powder for suspension at the dosages of 10, 10, and 20 milligrams/kilograms (mg/kg) at morning, midday, and evening, respectively for 48 weeks of treatment duration or until treatment discontinuation.	
Reporting group title	Placebo
Reporting group description: Participants received matching placebo orally at morning, midday, and evening for 48 weeks of treatment duration or until treatment discontinuation.	

### Primary: Absolute Change From Baseline in Percent-Predicted Forced Expiratory Volume in One Second (ppFEV1) at Week 48

End point title	Absolute Change From Baseline in Percent-Predicted Forced Expiratory Volume in One Second (ppFEV1) at Week 48
End point description: The FEV1 is the volume of air forcibly exhaled in 1 second and is measured using forced expiratory air spirometry. Change in ppFEV1 at Week 48 was defined as the average between the change from baseline at Week 40 and that at Week 48. Baseline for ppFEV1 was defined as an average of ppFEV1 at Screening (Weeks -4 to -1) and Baseline (Day 1) visits. The intent-to-treat (ITT) population included all randomized participants who had FEV1 data available at Baseline and at least 1 post-baseline visit.	
End point type	Primary
End point timeframe: From Baseline to Week 48	

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	136		
Units: Percentage of predicted FEV1				
least squares mean (confidence interval 95%)	-1.396 (-2.7735 to -0.0180)	-1.992 (-3.3271 to -0.6576)		

### Statistical analyses

Statistical analysis title	Ataluren versus Placebo
Comparison groups	Ataluren v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5336
Method	Mixed-model, repeated-measures
Parameter estimate	Mean difference (net)
Point estimate	0.597

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2881
upper limit	2.4813
Variability estimate	Standard error of the mean
Dispersion value	0.957

### Secondary: 48-Week Rate of Pulmonary Exacerbations

End point title	48-Week Rate of Pulmonary Exacerbations
-----------------	---

End point description:

Pulmonary exacerbations were assessed using expanded Fuchs' criteria. The expanded Fuchs' exacerbation is defined as the presence of at least 4 of 12 Fuchs' signs and symptoms requiring treatment with any form of antibiotic treatment (inhaled, oral, or intravenous). Fuchs' signs and symptoms included increased cough; change in sputum volume, color, or consistency; new or increased hemoptysis; increased dyspnea during moderate or mild exertion, or at rest; sinus pain or tenderness; change in sinus discharge; malaise, fatigue, or lethargy; anorexia or weight loss; temperature above 38 degrees Celsius; change in findings on chest examination; relative 10% decrease in ppFEV1, and chest radiography results consistent with pulmonary infection. The 48-week rate was calculated as: 48-week rate = total number of events/treatment duration by Week 48. The ITT population included all randomized participants who had FEV1 data available at Baseline and at least 1 post-baseline visit.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 48

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	136		
Units: number of exacerbations per 48 weeks				
arithmetic mean (standard deviation)	0.950 (± 1.4038)	1.127 (± 2.5241)		

### Statistical analyses

<b>Statistical analysis title</b>	Ataluren versus Placebo
Comparison groups	Ataluren v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4008
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.8567

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5973
upper limit	1.2288
Variability estimate	Standard error of the mean
Dispersion value	0.1577

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

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

End point description:

The teen/adult CFQ-R was used for this study. It was developed specifically for participants with cystic fibrosis. It is a disease-specific instrument designed to measure impact on overall health, daily life, perceived well-being, and symptoms. The respiratory domain assessed respiratory symptoms like coughing, congestion, wheezing etc. Scaling of each item is done via 4-point Likert scales. Scores for each item are summed up to generate a domain score. Scores ranges from 0 to 100, with higher scores indicating better health and lower scores indicating worse health. The ITT population included all randomized participants who had FEV1 data available at Baseline and at least 1 post-baseline visit.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 48

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	136		
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.760 (-3.4566 to 1.9364)	-1.032 (-3.7368 to 1.6728)		

### Statistical analyses

<b>Statistical analysis title</b>	Ataluren versus Placebo
Comparison groups	Ataluren v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8881
Method	Mixed-model, repeated measures
Parameter estimate	Median difference (net)
Point estimate	0.272

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5292
upper limit	4.0731
Variability estimate	Standard error of the mean
Dispersion value	1.93

### Secondary: Change From Baseline in Body Mass Index (BMI) at Week 48

End point title	Change From Baseline in Body Mass Index (BMI) at Week 48
End point description:	
Malnutrition is common in participants with cystic fibrosis. The BMI is an important clinical measure of nutritional status. The ITT population included all randomized participants who had FEV1 data available at Baseline and at least 1 post-baseline visit.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) and Week 48	

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	136		
Units: kilogram per meter square (kg/m <sup>2</sup> )				
least squares mean (confidence interval 95%)	0.296 (0.1126 to 0.4789)	0.361 (0.1759 to 0.5455)		

### Statistical analyses

Statistical analysis title	Ataluren versus Placebo
Comparison groups	Ataluren v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6208
Method	Mixed-model, repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3233
upper limit	0.1934
Variability estimate	Standard error of the mean
Dispersion value	0.1312

---

**Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs)**

---

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs)
-----------------	--

End point description:

Adverse Event (AE): any unfavourable/unintended sign, symptom or disease temporally associated with use of study drug, whether or not considered related to study treatment. TEAE: an AE that occurs or worsens in the period extending from first dose of study drug to 4 weeks after last dose of study drug. SAE: a TEAE, regardless of whether it is considered to be related to study drug resulting in 1 of following: death; inpatient hospitalization or prolongation of existing hospitalization; life-threatening; persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions; any other medically important event; or a pregnancy resulting in spontaneous abortion, stillbirth, neonatal death or congenital anomaly. A summary of serious and all other non-serious AEs regardless of causality is located in the Reported Adverse Events module. As-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post treatment follow-up visit (approximately 52 weeks)

---

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants				
TEAEs	133	135		
SAEs	40	46		

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Number of Participants with TEAEs by Severity and Relationship to Study Drugs**

---

End point title	Number of Participants with TEAEs by Severity and Relationship to Study Drugs
-----------------	---

End point description:

The relationship of TEAEs to the study drugs were assessed as: probable related, possibly related, unlikely related, and unrelated. The severity of TEAEs was graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 as: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal). A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. The as-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 weeks)

---

<b>End point values</b>	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants				
Severity: Grade 1	26	18		
Severity: Grade 2	88	88		
Severity: Grade 3	19	29		
Severity: Grade 4	0	0		
Severity: Grade 5	0	0		
Relationship to study drug: Unrelated	74	72		
Relationship to study drug: Unlikely related	37	34		
Relationship to study drug: Possible related	21	25		
Relationship to study drug: Probable related	1	4		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with SAEs by Relationship and Severity to Study Drugs

End point title	Number of Participants with SAEs by Relationship and Severity to Study Drugs
-----------------	--

End point description:

The relationship of SAEs to the study drugs was assessed as: probable related, possibly related, unlikely related, and unrelated. The severity of SAEs were graded using the CTCAE, Version 3.0 as: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal). A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. The as-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 weeks)

<b>End point values</b>	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants				
Severity: Grade 1	2	1		
Severity: Grade 2	23	20		
Severity: Grade 3	15	25		
Severity: Grade 4	0	0		
Severity: Grade 5	0	0		

Relationship to study drug: Unrelated	26	31		
Relationship to study drug: Unlikely related	13	15		
Relationship to study drug: Possible related	1	0		
Relationship to study drug: Probable related	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Abnormal Vital Signs Reported as TEAEs

End point title	Number of Participants with Abnormal Vital Signs Reported as TEAEs
-----------------	--

End point description:

Vital signs included systolic and diastolic blood pressure, pulse rate, pulse oximetry, and body temperature. Participants with abnormal vital signs who required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test), unless they are associated with an already reported clinical event, are reported. A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. The as-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 weeks)

End point values	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants	0	1		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants with Abnormal Clinical Laboratory Parameters Reported as TEAEs
-----------------	---

End point description:

Clinical laboratory tests included haematology, biochemistry, and urinalysis. Participants with abnormal laboratory parameters who required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test), unless they are associated with an already reported clinical event, are reported. A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. The as-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 weeks)

<b>End point values</b>	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants	32	30		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Abnormal Electrocardiogram Reported as TEAEs

End point title	Number of Participants with Abnormal Electrocardiogram Reported as TEAEs
-----------------	--

End point description:

Participants with abnormal electrocardiogram who required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test), unless they are associated with an already reported clinical event, are reported. A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. The as-treated population included all randomized participants who actually received any study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 weeks)

<b>End point values</b>	Ataluren	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	139		
Units: participants	1	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From study drug administration to 4-week post-treatment follow-up visit (approximately 52 Weeks)

Adverse event reporting additional description:

All randomized participants who actually received any study treatment were analysed for AEs and SAEs.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

### Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received matching placebo orally at morning, midday, and evening for 48 weeks of treatment duration or until treatment discontinuation.

Reporting group title	Ataluren
-----------------------	----------

Reporting group description:

Participants received ataluren as oral powder for suspension at the dosages of 10, 10, and 20-mg/kg at morning, midday, and evening, respectively for 48 weeks of treatment duration or until treatment discontinuation.

<b>Serious adverse events</b>	Placebo	Ataluren	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 139 (33.09%)	40 / 140 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pseudocholinesterase deficiency			

subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
Thrombosis in device			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Constipation			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
Bronchopneumopathy			

subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cough</b>			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haemoptysis</b>			
subjects affected / exposed	1 / 139 (0.72%)	4 / 140 (2.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nasal polyps</b>			
subjects affected / exposed	1 / 139 (0.72%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumothorax spontaneous</b>			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Tachypnoea</b>			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Red man syndrome</b>			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Psychiatric disorders</b>			
<b>Suicidal ideation</b>			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			

Nephrolithiasis			
subjects affected / exposed	0 / 139 (0.00%)	3 / 140 (2.14%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
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			
Costochondritis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device-related sepsis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	34 / 139 (24.46%)	25 / 140 (17.86%)
occurrences causally related to treatment / all	0 / 50	2 / 36
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Mycobacterium abscessus infection</b>		
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Peritonitis</b>		
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Pneumonia</b>		
subjects affected / exposed	2 / 139 (1.44%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Pneumonia influenzal</b>		
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Pneumonia staphylococcal</b>		
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Pseudomonas infection</b>		
subjects affected / exposed	0 / 139 (0.00%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Respiratory tract infection</b>		
subjects affected / exposed	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Respiratory tract infection fungal</b>		

subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 139 (0.72%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 139 (1.44%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 139 (0.72%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 139 (0.72%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Ataluren	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 139 (86.33%)	123 / 140 (87.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 139 (11.51%)	12 / 140 (8.57%)	
occurrences (all)	18	23	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 139 (7.19%)	9 / 140 (6.43%)	
occurrences (all)	12	17	
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	5 / 139 (3.60%) 6	11 / 140 (7.86%) 15	
Diarrhoea subjects affected / exposed occurrences (all)	12 / 139 (8.63%) 20	13 / 140 (9.29%) 15	
Nausea subjects affected / exposed occurrences (all)	10 / 139 (7.19%) 12	11 / 140 (7.86%) 14	
Vomiting subjects affected / exposed occurrences (all)	4 / 139 (2.88%) 7	8 / 140 (5.71%) 8	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	25 / 139 (17.99%) 31	25 / 140 (17.86%) 36	
Haemoptysis subjects affected / exposed occurrences (all)	10 / 139 (7.19%) 22	12 / 140 (8.57%) 17	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 139 (2.16%) 7	7 / 140 (5.00%) 7	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	78 / 139 (56.12%) 145	75 / 140 (53.57%) 142	
Influenza subjects affected / exposed occurrences (all)	8 / 139 (5.76%) 9	7 / 140 (5.00%) 7	
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 139 (5.76%) 10	10 / 140 (7.14%) 13	
Pharyngitis			

subjects affected / exposed occurrences (all)	2 / 139 (1.44%) 3	7 / 140 (5.00%) 8
Pseudomonas infection subjects affected / exposed occurrences (all)	9 / 139 (6.47%) 10	4 / 140 (2.86%) 4
Rhinitis subjects affected / exposed occurrences (all)	8 / 139 (5.76%) 9	10 / 140 (7.14%) 12
Sinusitis subjects affected / exposed occurrences (all)	11 / 139 (7.91%) 11	16 / 140 (11.43%) 20
Staphylococcal infection subjects affected / exposed occurrences (all)	8 / 139 (5.76%) 9	4 / 140 (2.86%) 4
Upper respiratory tract infection subjects affected / exposed occurrences (all)	21 / 139 (15.11%) 26	21 / 140 (15.00%) 25
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	21 / 139 (15.11%) 25	27 / 140 (19.29%) 43

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2014	<ul style="list-style-type: none"><li>• Updated the required screening laboratory values; the previous requirement of plasma adrenocorticotrophic hormone (ACTH) <math>\leq</math> upper limit of normal (ULN) in the adrenal system has been removed.<ul style="list-style-type: none"><li>- The ACTH laboratory parameter, as an indicator of cortisol cycle and hypothalamus-pituitary-adrenal axis function, was found to be obsolete, and had been a legacy from earlier studies (in which no relevant change had been found).</li></ul></li> <li>• Updated exclusion criteria for chronic use of inhaled or systemic tobramycin within 4 weeks prior to screening; change in acute therapy between screening and randomization; and evidence of pulmonary exacerbation between screening and randomization.<ul style="list-style-type: none"><li>- The previous, longer, 4-month exclusion of inhaled or systemic tobramycin, was found to be impractical, and an impediment to enrolment.</li><li>- The 4-week exclusion of inhaled or systemic tobramycin allows for a more "lifelike, standard of care" approach, in which Investigators treat possible P.aeruginosa lung infection in the way they would in normal clinical routine.</li><li>- A possible interference between tobramycin and ataluren regarding read through in nonsense mutations is believed to be fully washed out at 1-2 weeks (that is, less than 1 month).</li></ul></li> <li>• Identified the type of medications that must be withheld for at least 4 hours prior to spirometric tests; explanation of the timing of restrictions on short- and long-acting beta agonists was added.<ul style="list-style-type: none"><li>- Short-acting beta agonists (SABA) are routinely withheld prior to lung function for 4 hours (long-acting beta agonists [LABA] are routinely withheld for 12 hours prior to lung function), and with the above clarification in the protocol, this was included in the participant materials.</li></ul></li></ul>
30 September 2016	<ul style="list-style-type: none"><li>• Changed the primary endpoint from relative to absolute change in ppFEV1 and redefined the change at Week 48 as an average between the change at Weeks 40 and 48, as per feedback from regulatory authorities.</li> <li>• Updated the definition of pulmonary exacerbation to use the Expanded Fuchs' criteria instead of the Modified Fuchs' criteria based on the most current clinical information.</li> <li>• Revised BMI and CFQ-R respiratory domain as secondary endpoints (previously tertiary endpoints).</li> <li>• Added additional tertiary endpoints:<ul style="list-style-type: none"><li>- Time to pulmonary exacerbations.</li><li>- Incidence of pulmonary exacerbations requiring hospitalization.</li><li>- Change in weight and height.</li><li>- Incidence and rate of disruptions to daily living (for example, missed school or work).</li><li>- Incidence, rate, and duration (where possible) of interventions (for example, antibiotic use and hospitalization).</li><li>- Adjusted sample size calculations based on the new primary endpoint, explained the hierarchical testing procedure for the secondary endpoints, and detailed the statistical analysis plan (SAP) for the newly added endpoints.</li></ul></li></ul>

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported