Clinical trial results:
A Phase 2 Study of PTC124 as an Oral Treatment for Nonsense-Mutation-Mediated Cystic Fibrosis

Summary

EudraCT number	2007-000724-40
Trial protocol	BE
Global end of trial date	29 February 2008

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-006-CF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00458341
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)	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	21 December 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2008
Global end of trial reached?	Yes
Global end of trial date	29 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine whether PTC124 safely provides pharmacologic activity as evaluated by transepithelial potential difference (TEPD) assessment of cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride transport.

Protection of trial subjects:

The trial was conducted in accordance with Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000) and the International Conference on Harmonisation (ICH) GCP guidance documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2007
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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 22
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	11
Adolescents (12-17 years)	18
Adults (18-64 years)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized so that half received the lower-dose level in Cycle 1 and then the higher-dose level in Cycle 2 (low-to-high dose sequence) and half received the higher-dose level in Cycle 1 and then the lower-dose level in Cycle 2 (high-to-low dose sequence).

Period 1

Period 1 title	Cycle 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg

Arm description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	PTC124
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.

Arm title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg

Arm description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	PTC124
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.

Number of subjects in period 1	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg
Started	15	15
Received at Least 1 Dose of Study Drug	15	15
Completed	14	15
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Cycle 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg

Arm description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	PTC124
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.

Arm title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg

Arm description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	PTC124
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.

Number of subjects in period 2	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg
Started	14	15
Received at Least 1 Dose of Study Drug	15	15
Completed	15	15

Joined	1	0
Participant who didn’t complete C1 eligible for C2	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cycle 1

Reporting group description: -

Reporting group values	Cycle 1	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	11	11	
Adolescents (12-17 years)	18	18	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	12.5		
standard deviation	± 3.43	-	
Sex: Female, Male Units: Subjects			
Female	14	14	
Male	16	16	

Subject analysis sets

Subject analysis set title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Subject analysis set title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Reporting group values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	5	
Adolescents (12-17 years)	9	9	
Adults (18-64 years)	0	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	12	13	
standard deviation	± 3.53	± 3.38	
Sex: Female, Male Units: Subjects			
Female	6	8	
Male	9	7	

End points

End points reporting groups

Reporting group title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg

Reporting group description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Reporting group title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg

Reporting group description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Reporting group title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg

Reporting group description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Reporting group title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg

Reporting group description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Subject analysis set title	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

During Cycle 1, participants received ataluren at 4 milligrams (mg/kg) in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 10, 10, and 20 mg/kg) for Cycle 2.

Subject analysis set title	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

During Cycle 1, participants received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by a 14-day follow-up period without treatment. Then, the participants crossed over to the other ataluren dose regimen (ataluren 4, 4, and 8 mg/kg) for Cycle 2.

Primary: Change From Baseline in Total Chloride Transport at Day 14 of Cycles 1 and 2

End point title	Change From Baseline in Total Chloride Transport at Day 14 of Cycles 1 and 2[1]

End point description:

TEPD assessed in each participant. Warmed solutions of Ringer's solution, amiloride, chloride-free gluconate, isoproterenol, and adenosine triphosphate (ATP) were perfused through a nasal catheter while a voltage tracing was recorded. Total chloride transport computed for each nostril. The total chloride transport values calculated by subtracting the voltages at the end of a perfusion from the voltage at the end of an earlier perfusion (isoproterenol-amiloride). Population included randomized participants receiving ≥1 dose of study drug with evaluable chloride transport data. Baseline data for Cycles 1 and 2 and change from Baseline data at Day 14 of Cycles 1 and 2 are presented. Via a 2-sided t-test, the Baseline of Cycle 1 vs Day 14 of Cycle 1 at Ataluren 4, 4, and 8 mg/kg p-value=0.133 and at Ataluren 10, 10, and 20 mg/kg p-value=0.190 and the Baseline of Cycle 2 vs Day 14 of Cycle 2 at Ataluren 4, 4, and 8 mg/kg p-value=0.123 and at Ataluren 10, 10, and 20 mg/kg p-value=0.592.

End point type	Primary

End point timeframe:

Baseline of Cycle 1 and Cycle 2, Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days)

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: Due to database restrictions, statistical analysis data are presented in the Endpoint Description.

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: millivolts (mV)				
arithmetic mean (standard deviation)				
Baseline of Cycle 1 (N=15, 15)	1.45 (± 5.671)	0.66 (± 4.563)		
Change at Day 14 of Cycle 1 (N=14, 14)	-2.81 (± 6.543)	-2.69 (± 7.289)		
Baseline of Cycle 2 (N=15, 13)	-0.92 (± 4.474)	-3.76 (± 6.729)		
Change at Day 14 of Cycle 2 (N=14, 13)	-2.39 (± 5.426)	1.10 (± 7.179)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With a Chloride Transport Response at Day 14 of Cycles 1 and 2

End point title	Number of Participants With a Chloride Transport Response at Day 14 of Cycles 1 and 2[2]

End point description:

Nasal TEPD assessed in each participant. Warmed solutions of Ringer’s solution, amiloride, chloride-free gluconate, isoproterenol, and ATP perfused through a nasal catheter while a voltage tracing was recorded. Total chloride transport computed for each nostril. Total chloride transport values calculated by subtracting the voltages at the end of a perfusion from the voltage at the end of an earlier perfusion (isoproterenol-amiloride). Response to study treatment defined as an increase in total chloride transport as indicated by a change of at least -5 mV in nasal TEPD. Population included randomized participants receiving ≥1 dose of study drug with evaluable chloride transport data. Via a chi-squared test, the observed rate with the null hypothesis response rate of 10% for Cycle 1 at Ataluren 4, 4, and 8 mg/kg p-value=0.021 and at Ataluren 10, 10, and 20 mg/kg p-value=0.021 and for Cycle 2 at Ataluren 4, 4, and 8 mg/kg p-value=0.021 and at Ataluren 10, 10, and 20 mg/kg p-value=0.518.

End point type	Primary

End point timeframe:

Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days)

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: Due to database restrictions, statistical analysis data are presented in the Endpoint Description.

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: participants				
Day 14 of Cycle 1 (n=14, 14)	4	4		
Day 14 of Cycle 2 (n=14, 13)	4	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Normalization of Chloride Transport Between Baseline and Day 14 of Cycles 1 and 2

End point title	Number of Participants With Normalization of Chloride Transport Between Baseline and Day 14 of Cycles 1 and 2[3]

End point description:

Nasal TEPD was assessed in each participant using standardized techniques. Warmed solutions of Ringer's solution, amiloride, chloride-free gluconate, isoproterenol, and 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. Normalization of chloride transport (normal range [NR]) was defined as nasal TEPD that was at least as electrically negative as -5 mV. Population included all randomized participants who received at least 1 dose of study drug and had evaluable normalization of chloride transport data.

End point type	Primary

End point timeframe:

Overall Baseline and Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days)

Notes:

[3] - 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: Due to database restrictions, statistical analysis data are presented in the Endpoint Description.

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14		
Units: participants				
Within NR at Baseline of Cycle (C)1 (n=14, 14)	0	0		
Within NR at Day (D)14 of Cycle 1 (n=14, 14)	1	5		
Outside NR at Baseline/in NR at D14, C1 (n=14, 14)	1	5		
Within NR at Baseline of C2 (n=14, 13)	2	4		
Within NR at D14 of C2 (n=14, 13)	6	3		

Outside NR at Baseline/in NR at D14, C2 (n=14, 13)	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parameters of Transepithelial Difference at Day 14 of Cycles 1 and 2

End point title	Change From Baseline in Parameters of Transepithelial Difference at Day 14 of Cycles 1 and 2

End point description:

To assess TEPD, warmed solutions of Ringer's solution, amiloride, chloride-free gluconate, isoproterenol and ATP were perfused for ≥3-minutes sequentially through a nasal catheter while a voltage tracing was recorded. Total chloride transport was computed per nostril. Totals were calculated by subtracting voltages at end of perfusion from voltage at end of earlier perfusion for: sodium transport (amiloride–Ringer's solution), intrinsic chloride transport (CL trans) (chloride-free gluconate–amiloride), stimulated CL trans (isoproterenol–chloride-free gluconate), total potential difference (dif) (isoproterenol–Ringer's solution), and ATP-mediated CL trans (ATP–isoproterenol). Basal potential dif voltage was obtained at end of Ringer's solution perfusion. Population included all randomized participants who received at least 1 dose of study drug and had evaluable transepithelial difference data.

End point type	Secondary

End point timeframe:

Baseline of Cycle 1 and Cycle 2, Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days)

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: mV				
arithmetic mean (standard deviation)				
Basal nasal TEPD, Baseline of C1 (n=15, 15)	-53.91 (± 18.81)	-56.51 (± 20.68)		
Basal nasal TEPD, Change at D14 of C1 (n=14, 14)	9.31 (± 17.72)	-3.70 (± 13.33)		
Basal nasal TEPD, Baseline of C2 (n=15, 13)	-46.28 (± 14.46)	-50.02 (± 17.09)		
Basal nasal TEPD, Change at D14 of C2 (n=14, 13)	-6.31 (± 19.33)	-5.22 (± 24.48)		
Sodium transport, Baseline of C1 (n=15, 15)	34.38 (± 17.72)	36.40 (± 18.44)		
Sodium transport, Change at D14 of C1 (n=14, 14)	-4.97 (± 15.30)	1.55 (± 18.39)		
Sodium transport, Baseline of C2 (n=15, 13)	28.85 (± 14.31)	32.15 (± 17.72)		
Sodium transport, Change at D14 of C2 (n=14, 13)	6.38 (± 19.81)	5.50 (± 20.69)		
Intrinsic CL trans, Baseline of C1 (n=15, 15)	2.38 (± 4.19)	1.11 (± 4.01)		

Intrinsic CL trans, Change at D14 of C1 (n=14, 14)	-2.54 (± 4.70)	-2.69 (± 4.96)		
Intrinsic CL trans, Baseline of C2 (n=15, 13)	-1.32 (± 5.61)	-0.90 (± 3.44)		
Intrinsic CL trans, Change at D14 of C2 (n=14, 13)	-1.20 (± 6.23)	-1.12 (± 5.34)		
Stimulated CL trans, Baseline of C1 (n=15, 15)	-0.93 (± 2.22)	-0.45 (± 1.63)		
Stimulated CL trans, Change at D14 C1(n=14, 14)	-0.27 (± 3.44)	0 (± 4.26)		
Stimulated CL trans, Baseline of C2 (n=15, 13)	0.40 (± 4.83)	-2.86 (± 6.98)		
Stimulated CL trans, Change at D14 C2 (n=14,13)	-1.19 (± 5.89)	2.21 (± 8.77)		
Total potential dif, Baseline of C1 (n=14, 15)	35.83 (± 17.25)	37.06 (± 17.25)		
Total potential dif, Change at D14 C1 (n=15, 14)	-7.77 (± 12.16)	-1.14 (± 13.89)		
Total potential dif, Baseline of C2 (n=15, 15)	27.93 (± 15.37)	28.39 (± 17.18)		
Total potential dif, Change at D14 C2 (n=14, 13)	3.99 (± 19.48)	6.59 (± 20.20)		
ATP-mediated CL trans, Baseline C1 (n=11, 11)	-19.84 (± 10.22)	-17.65 (± 10.62)		
ATP-mediated CL trans, Change at D14, C1(n=10, 10)	4.93 (± 11.56)	-2.95 (± 15.59)		
ATP-mediated CL trans, Baseline C2 (n=11, 10)	-16.87 (± 13.24)	-16.34 (± 12.35)		
ATP-mediated CL trans, Change at D14C2(n=9, 10)	-0.38 (± 17.47)	-4.58 (± 27.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CFTR Protein in Nasal Mucosa as Determined by Immunofluorescence at Overall Day 56

End point title	Change From Baseline in CFTR Protein in Nasal Mucosa as Determined by Immunofluorescence at Overall Day 56

End point description:

The immunofluorescence staining of normal epithelial cells (for example, from nasal mucosal curettage) reveals the presence of cystic fibrosis transmembrane regulator (CFTR) protein at the apical surface. Cells were stained with antibodies that recognized an epitope in the C-terminal portion of the CFTR protein, and the cells were imaged microscopically. The percentage of epithelial cells that showed apical CFTR staining was determined by 2 expert readers who were blinded to the timepoint at which the samples were obtained. The scores of the reviewers were averaged to determine the final percentage of cells with apical CFTR. Population included all randomized participants who received at least 1 dose of study drug and had evaluable apical cell data. Overall Baseline data for the study and change from overall Baseline data at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	11		
Units: percentage of apical cells				
arithmetic mean (standard deviation)				
Overall Baseline (n=12, 11) Change at Overall Day 56 (n=10, 11)	15.95 (± 16.797) 10.45 (± 24.337)	10.47 (± 9.270) 22.89 (± 29.389)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Nonsense Mutation CFTR mRNA in Nasal Mucosa as Determined by Quantitative Real-Time Polymerase Chain Reaction (RT-PCR) Assay at Overall Day 42

End point title	Change From Baseline in Nonsense Mutation CFTR mRNA in Nasal Mucosa as Determined by Quantitative Real-Time Polymerase Chain Reaction (RT-PCR) Assay at Overall Day 42

End point description:

The collection and processing of the nasal mucosal curettage from each nostril of each participant for measurement of CFTR protein by immunofluorescence and for quantification of CFTR messenger ribonucleic acid (mRNA) was performed using standardized techniques. The slides were processed and immunostained for detection of CFTR protein. Microscopic images were to be captured photographically for analysis. Because the nasal brushing used to collect nasal mucosal epithelial cells did not result in collection of sufficient cells for RT-PCR to be performed, an insufficient number of paired baseline and follow-up samples were available for analysis. As a result, no data were available to evaluate the effects of ataluren on CFTR mRNA. Population included all randomized participants who received at least 1 dose of study drug and had evaluable CFTR mRNA data.

End point type	Secondary

End point timeframe:

Overall Baseline, Overall Day 42

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[4]	0[5]		
Units: percent change				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - No data are available to evaluate the effects of ataluren on CFTR mRNA.

[5] - No data are available to evaluate the effects of ataluren on CFTR mRNA.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Function as Measured by Spirometry at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Pulmonary Function as Measured by Spirometry at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

Pulmonary function tests, including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and forced expiratory flow25-75 (FEF25-75), were measured using standard spirometry techniques. Overall Baseline data for the study and change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented. Population included all randomized participants who received at least 1 dose of study drug and had evaluable pulmonary function data.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: percent of predicted				
arithmetic mean (standard deviation)				
FEV1, Overall Baseline (n=15, 15)	92.68 (± 22.645)	85.14 (± 27.850)		
FEV1, Change at D14/15 of C1 (n=14, 15)	2.73 (± 5.848)	-4.60 (± 7.579)		
FEV1, Change at D14/15 of C2 (n=15, 15)	-0.46 (± 11.031)	0.02 (± 8.801)		
FEV1, Change at Overall Day 56 (n=15, 15)	-0.36 (± 12.936)	-0.39 (± 8.191)		
FVC, Overall Baseline (n=15, 15)	101.83 (± 13.294)	95.34 (± 22.515)		
FVC, Change at D14/15 of C1 (n=14, 15)	2.52 (± 7.216)	-2.33 (± 6.643)		
FVC, Change at D14/15 of C2 (n=15, 15)	-0.44 (± 7.433)	-0.44 (± 7.433)		
FVC, Change at Overall Day 56 (n=15, 15)	-0.65 (± 9.117)	1.02 (± 6.796)		
FEF 25-75%, Overall Baseline (n=15, 15)	88.32 (± 49.740)	71.20 (± 41.194)		
FEF 25-75%, Change at D14/15 of C1 (n=14, 15)	2.98 (± 19.679)	-3.63 (± 12.300)		
FEF 25-75%, Change at D14/15 of C2 (n=15, 15)	3.19 (± 22.712)	-0.39 (± 19.192)		
FEF 25-75%, Change at Overall Day 56 (n=15, 15)	-2.76 (± 27.406)	-4.29 (± 23.379)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sputum Markers of Inflammation (Free Elastase) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Sputum Markers of Inflammation (Free Elastase) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

The inflammatory marker free elastase was measured in induced sputum from each participant. Hypertonic saline (3%) inhalation was used to induce the sputum (with efforts made to avoid oropharyngeal contamination). The sputum sample was divided into 4 aliquots (1 aliquot each for determination of cell count, IL-8 level, and elastase activity and 1 aliquot for potential future viscosity measurements). Population included all randomized participants who received at least 1 dose of study drug and had evaluable sputum markers of inflammation data. Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	10		
Units: micrograms/milliliters (µg/mL)				
arithmetic mean (standard deviation)				
Free Elastase, Baseline (n=12, 10)	108.85 (± 107.617)	60.92 (± 56.170)		
Free Elastase, Change at D14/15 of C1 (n=10, 10)	-37.78 (± 95.154)	74.66 (± 83.258)		
Free Elastase, Change at D14/15 of C2 (n=9, 10)	-24.40 (± 93.804)	37.33 (± 65.240)		
Free Elastase, Change at Overall Day 56 (n=9, 10)	12.47 (± 84.427)	57.18 (± 139.211)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sputum Markers of Inflammation (Matrix Metalloproteinase 9 [MMP-9] active) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Sputum Markers of Inflammation (Matrix Metalloproteinase 9 [MMP-9] active) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

The inflammatory marker MMP-9 active was measured in induced sputum from each participant. Hypertonic saline (3%) inhalation was used to induce the sputum (with efforts made to avoid oropharyngeal contamination). The sputum sample was divided into 4 aliquots (1 aliquot each for determination of cell count, IL-8 level, and elastase activity and 1 aliquot for potential future viscosity measurements). Population included all randomized participants who received at least 1 dose of study

drug and had evaluable sputum markers of inflammation data. Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: nanograms/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
MMP-9 Active, Baseline (N=13, 15)	69431.28 (± 109894.966)	20908.56 (± 28441.612)		
MMP-9 Active, Change at D14/15 of C1 (n=11, 10)	-44527.45 (± 92493.455)	71639.89 (± 150716.037)		
MMP-9 Active, Change at D14/15 of C2 (n=11, 10)	-51330.37 (± 108057.265)	14947.54 (± 69337.080)		
MMP-9 Active, Change at Overall Day 56 (n=10, 10)	-49644.49 (± 86334.812)	56884.39 (± 158498.793)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sputum Markers of Inflammation (Tumor Necrosis Factor-Alpha [TNF-α], Interleukin-8 [IL-8], Transforming Growth Factor Beta 1 [TGF-β1]) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Sputum Markers of Inflammation (Tumor Necrosis Factor-Alpha [TNF-α], Interleukin-8 [IL-8], Transforming Growth Factor Beta 1 [TGF-β1]) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

The inflammatory markers TNF-α, IL-8, and TGF-β1 were measured in induced sputum from each participant. Hypertonic saline (3%) inhalation was used to induce the sputum (with efforts made to avoid oropharyngeal contamination). The sputum sample was divided into 4 aliquots (1 aliquot each for determination of cell count, IL-8 level, and elastase activity and 1 aliquot for potential future viscosity measurements). Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	10		
Units: picograms/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
IL-8, Baseline (N=13, 10)	352539.57 (± 331865.227)	121879.75 (± 83684.594)		
IL-8, Change at Day 14/15 of Cycle 1 (n=11, 10)	-171764.67 (± 296343.195)	98483.55 (± 154432.714)		
IL-8, Change at Day 14/15 of Cycle 2 (n=11, 10)	-71206.95 (± 289379.557)	-4087.25 (± 127038.632)		
IL-8, Change at Overall Day 56 (n=10, 10)	-121626.94 (± 263731.747)	52880.35 (± 176223.116)		
TGF-b1, Baseline (N=12, 10)	80.84 (± 280.044)	322.56 (± 612.153)		
TGF-b1, Change at Day 14/15 of Cycle 1 (n=9, 10)	0 (± 0)	-322.56 (± 612.15)		
TGF-b1, Change at Day 14/15 of Cycle 2 (n=10, 9)	-97.01 (± 306.773)	-168.91 (± 774.276)		
TGF-b1, Change at Overall Day 56 (n=9, 7)	-61.32 (± 367.788)	-392.21 (± 771.006)		
TNF-alpha, Baseline (N=11, 8)	203.15 (± 185.530)	95.69 (± 139.550)		
TNF-alpha, Change at Day 14/15 of Cycle 1 (n=9, 8)	-58.94 (± 183.812)	46.38 (± 67.679)		
TNF-alpha, Change at Day 14/15 of Cycle 2 (n=9, 8)	-85.28 (± 123.341)	-58.45 (± 144.728)		
TNF-alpha, Change at Overall Day 56 (n=8, 8)	1.50 (± 267.702)	0.25 (± 122.285)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sputum Markers of Inflammation (Uridine-5'-triphosphate [UTP]) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Sputum Markers of Inflammation (Uridine-5'-triphosphate [UTP]) at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

The inflammatory marker UTP was measured in induced sputum from each participant. Hypertonic saline (3%) inhalation was used to induce the sputum (with efforts made to avoid oropharyngeal contamination). The sputum sample was divided into 4 aliquots (1 aliquot each for determination of cell count, IL-8 level, and elastase activity and 1 aliquot for potential future viscosity measurements). Population included all randomized participants who received at least 1 dose of study drug and had evaluable sputum markers of inflammation data. Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	10		
Units: milligrams/deciliter (mg/dL)				
arithmetic mean (standard deviation)				
UTP, Baseline (n=13, 10)	800.27 (± 509.794)	483.31 (± 222.102)		
UTP, Change at Day 14/15 of Cycle 1 (n=11, 10)	-202.85 (± 427.324)	411.50 (± 359.669)		
UTP, Change at Day 14/15 of Cycle 2 (n=11, 10)	-200.94 (± 549.730)	198.03 (± 436.888)		
UTP, Change at Overall Day 56 (n=10, 9)	-220.16 (± 414.258)	-15.86 (± 242.686)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinically Significant Neutrophil Levels in Blood at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Clinically Significant Neutrophil Levels in Blood at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

To assess inflammatory markers in the blood, neutrophil levels in the blood were measured. Higher levels of neutrophils are indicative of more inflammation. Population included all randomized participants who received at least 1 dose of study drug and had evaluable data of neutrophil levels in blood. Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: 10^9/liters				
arithmetic mean (standard deviation)				
Neutrophils - Absolute, Baseline	3.555 (± 1.2328)	4.709 (± 3.0884)		
Neutrophils - Absolute, D14/15 of C1 (n=14, 15)	-0.332 (± 1.3416)	-0.330 (± 2.7710)		

Neutrophils - Absolute, D14/15 of C 2 (n=15, 15)	-0.290 (± 1.4881)	-0.748 (± 2.2473)		
Neutrophils - Absolute, Overall Day 56 (n=15, 15)	-0.114 (± 1.4724)	-0.931 (± 2.7452)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinically Significant Serum Levels of C-Reactive Protein at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Clinically Significant Serum Levels of C-Reactive Protein at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point description:

To assess inflammatory markers in the blood, serum levels of C-reactive protein were measured. Higher levels of C-reactive protein are indicative of more inflammation. Population included all randomized participants who received at least 1 dose of study drug and had evaluable serum levels of C-reactive data. Change from overall Baseline data at Day 14 or 15 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 or 15 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: milligrams/liter (mg/L)				
arithmetic mean (standard deviation)				
C-Reactive Protein, Baseline (N=15, 15)	6.432 (± 4.9133)	8.273 (± 7.8838)		
C-Reactive Protein, D14/15 of C1 (n=14, 15)	-0.150 (± 1.6337)	7.059 (± 16.9563)		
C-Reactive Protein, D14/15 of C2 (n=15, 15)	-0.233 (± 0.7761)	2.933 (± 12.0167)		
C-Reactive Protein, Overall Day 56 (n=15, 15)	2.361 (± 7.4765)	1.240 (± 7.7170)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight at Day 14 or 15 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in Body Weight at Day 14 or 15 of

	Cycles 1 and 2 and Overall Day 56

End point description:

Body weight were measured for each participant in kilograms (kg). Population included all randomized participants who received at least 1 dose of study drug and had evaluable body weight data. Overall Baseline data for the study and change from overall Baseline data at Day 14 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: kg				
arithmetic mean (standard deviation)				
Overall Baseline (n=15, 15)	40.35 (± 12.239)	41.72 (± 11.435)		
Change at Day 14 of Cycle 1 (n=14, 15)	0.12 (± 1.064)	-0.01 (± 1.031)		
Change at Day 14 of Cycle 2 (n=15, 15)	0.37 (± 1.293)	0.03 (± 0.980)		
Change at Overall Day 56 (n=15, 15)	0.43 (± 1.278)	0.23 (± 1.528)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the CF-Related Symptom Scores, as Assessed Using a Participant-Reported Questionnaire at Day 14 of Cycles 1 and 2 and Overall Day 56

End point title	Change From Baseline in the CF-Related Symptom Scores, as Assessed Using a Participant-Reported Questionnaire at Day 14 of Cycles 1 and 2 and Overall Day 56

End point description:

The CF symptom self-reported (or their guardians) questionnaire includes questions related to daytime cough, nighttime cough, sputum volume, sputum clearance, physical fatigue, and shortness of breath. For each symptom, the participants were asked to choose the response that best matched their experience during the 3 days before the questionnaire was completed. The scale of the 4 possible responses for each question was 0 (best response) to 4 (worse response). The sum of the scores for all of the questions was calculated. The scale for the sum of the scores was 0 (best response) to 24 (worse response). Population included all randomized participants who received at least 1 dose of study drug and had evaluable CF-related symptom scores. Overall Baseline data for the study and change from overall Baseline data at Day 14 of Cycles 1 and 2 and at overall Day 56 are presented.

End point type	Secondary

End point timeframe:

Overall Baseline, Day 14 of Cycle 1 and Cycle 2 (1 cycle=28 days), and Overall Day 56

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: scores on a scale				
median (full range (min-max))				
Overall Baseline (n=15, 15)	14.0 (7 to 19)	11.0 (7 to 17)		
Change at Day 14 of Cycle 1 (n=14, 15)	-0.5 (-7 to 6)	0 (-5 to 4)		
Change at Day 14 of Cycle 2 (n=15, 14)	-1.0 (-5 to 7)	1.0 (-5 to 8)		
Change at Overall Day 56 (n=15, 15)	-1.0 (-7 to 9)	0 (-6 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under the Concentration Time Curve from Time 0 (Dosing) to 24 hours (AUC0-24) of Ataluren

End point title	PK: Area Under the Concentration Time Curve from Time 0 (Dosing) to 24 hours (AUC0-24) of Ataluren

End point description:

All PK parameters were calculated using the actual postdose blood sampling times in relationship to the time of the first dose (morning dose) on Day 14 of each treatment cycle. AUC0-24 values were calculated by WinNonlin by extrapolation to 24 hours if the last sampling timepoint was before 24 hours and by interpolation if the last sampling timepoint was after 24 hours. Extrapolation of AUC to 24 hours was performed only if the last sampling timepoint did not deviate from the nominal collection time by more than approximately 10%. Population included all randomized participants who received at least 1 dose of study drug and had evaluable AUC0-24 data. The data for each dose level represents pooled data for participants in the low-to-high dose sequence and the high-to-low dose sequence.

End point type	Secondary

End point timeframe:

0 (predose), 2 and 3 hours postdose of the morning dose; 0 (predose), 2 and 3 hours postdose of the midday dose; and 0 hours (predose), 2, 3, and 12 hours postdose of the evening dose on Day 14 of Cycle 1 and Cycle 2

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: microgram*hours/milliliter (µg*h/mL)				
arithmetic mean (standard error)	121.52 (± 9.79)	348.75 (± 21.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance with Study Treatment

End point title	Compliance with Study Treatment

End point description:

For each participant, compliance was described in terms of the percentage of drug actually taken relative to the amount that was prescribed (taking into account physician-prescribed reductions and interruptions). The number of doses described as "taken less than planned" includes cases in which the participants took less than the prescribed dose and/or cases in which the Investigator reduced the dose. Population included all randomized participants who received at least 1 dose of study drug and had evaluable compliance data. The data for each dose level represents pooled data for participants in the low-to-high dose sequence and the high-to-low dose sequence.

End point type	Secondary

End point timeframe:

Baseline up to Day 14 in Cycle 1 and Cycle 2

End point values	Ataluren 4, 4, and 8 mg/kg, then ataluren 10, 10, and 20 mg/kg	Ataluren 10, 10, and 20 mg/kg, then ataluren 4, 4, and 8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	30		
Units: percentage of doses				
median (full range (min-max))				
Percentage of doses taken as planned	97.50 (81.8 to 100.0)	100.0 (65.1 to 100.0)		
Percentage of doses missed	2.40 (0 to 15.8)	0 (0 to 16.2)		
Percentage of doses taken less than planned	0 (0 to 10.5)	0 (0 to 30.2)		
Percentage of doses taken greater than planned	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall Baseline up to Overall Day 56

Adverse event reporting additional description:

The data for each dose level represents pooled data for participants in the low-to-high dose sequence and the high-to-low dose sequence.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Ataluren Cohort 1

Reporting group description:

Participants in Cohort 1 received ataluren at 4 mg/kg in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days during Cycle 1 and received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days during Cycle 2. There was a 14-day follow up period without treatment in between Cycle 1 and Cycle 2.

Reporting group title	Ataluren Cohort 2

Reporting group description:

Participants in Cohort 2 received ataluren at 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days during Cycle 1 and received ataluren at 4 mg/kg in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 14 days during Cycle 2. There was a 14-day follow up period without treatment in between Cycle 1 and Cycle 2.

Serious adverse events	Ataluren Cohort 1	Ataluren Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cystic fibrosis pulmonary exacerbation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ataluren Cohort 1	Ataluren Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 30 (63.33%)	24 / 30 (80.00%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Asthenia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 30 (26.67%)	4 / 30 (13.33%)	
occurrences (all)	12	4	

Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Ascites			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Cystic fibrosis pulmonary exacerbation			
subjects affected / exposed	7 / 30 (23.33%)	4 / 30 (13.33%)	
occurrences (all)	9	4	
Haemoptysis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Productive cough			

subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Tendonitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	6 / 30 (20.00%)	5 / 30 (16.67%)	
occurrences (all)	8	8	
Stenotrophomonas infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported