Clinical trial results:
A Phase 3 Extension Study of Ataluren (PTC124) in Patients With Nonsense Mutation Dystrophinopathy

Summary

EudraCT number	2013-005489-20
Trial protocol	SE GB BE DE IT ES CZ FR BG
Global end of trial date	12 June 2018

Results information

Result version number	v1 (current)
This version publication date	02 August 2020
First version publication date	02 August 2020

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-020e-DMD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02090959
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	PTC Trial Disclosure, PTC Therapeutics, Inc., +353 19068700, ptctrialdisclosure@ptcbio.com
Scientific contact	PTC Trial Disclosure, PTC Therapeutics, Inc., +353 19068700, ptctrialdisclosure@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?	
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	12 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2018
Global end of trial reached?	Yes
Global end of trial date	12 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this extension study was to obtain long-term safety data of ataluren administered 3 times a day at 10, 10, and 20 milligrams/kilogram (mg/kg) to augment the ataluren safety database.

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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 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	Australia: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 63

Worldwide total number of subjects	218
EEA total number of subjects	95

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)	175
Adolescents (12-17 years)	43
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participants who successfully completed the double-blind, placebo-controlled Phase 3 study (PTC124-GD-020-DMD [NCT01826487]) were screened for this open-label extension study.

Pre-assignment

Screening details:

A total of 221 participants completed the double-blind Phase 3 Study PTC124-GD-020-DMD. Of the 221 participants who completed Study PTC124-GD-020-DMD, 219 participants were enrolled in this open-label extension study and 218 were treated.

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), 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for up to 144 weeks.

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

Dosage and administration details:

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

Number of subjects in period 1	Ataluren
Started	218
Completed	68
Not completed	150
Switched to commercial supply	88
Consent withdrawn by subject	10
Move to medical need program	3
Adverse event, non-fatal	1
Study termination	6
Investigator decision	2
Transfer for compassionate use medicine	4
Other than specified	2

Entered in to other study	34

Baseline characteristics

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Participants received ataluren suspension orally 3 times a day (TID), 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for up to 144 weeks.	

Reporting group values	Ataluren	Total	
Number of subjects	218	218	
Age categorical Units: Subjects			
Children (2-11 years)	175	175	
Adolescents (12-17 years)	43	43	
Age Continuous Units: years			
arithmetic mean	9.9		
standard deviation	± 1.78	-	
Sex: Female, Male Units: Subjects			
Female	0	0	
Male	218	218	
Race/Ethnicity, Customized Units: Subjects			
White	169	169	
Black	2	2	
Asian	13	13	
Hispanic	12	12	
Other	8	8	
Missing	14	14	
6 Minute Walk Distance (6MWD)			
The 6MWD test was performed in a 30 meters long flat corridor, where the participant was instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Ambulation was assessed via the 6MWD test following standardized procedures by measuring the 6MWD in meters. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWD test. Number of participants analyzed for this baseline measure are 198 (ambulatory participants).			
Units: meters			
arithmetic mean	349.885		
standard deviation	± 105.7913	-	
Time to Stand From Supine Position			
Number of participants analyzed for this baseline measure are 199.			
Units: seconds			
arithmetic mean	13.0		
standard deviation	± 10.34	-	
Time to Walk/Run 10 Meters			
Number of participants analyzed for this baseline measure are 215.			
Units: seconds			
arithmetic mean	9.31		
standard deviation	± 7.388	-	

Time to Climb 4 Stairs			
Number of participants analyzed for this baseline measure are 203.			
Units: seconds			
arithmetic mean	9.03		
standard deviation	± 8.939	-	
Time to Descend 4 Stairs			
Number of participants analyzed for this baseline measure are 204.			
Units: seconds			
arithmetic mean	7.52		
standard deviation	± 8.401	-	
North Star Ambulatory Assessment (NSAA) Total Score			
NSAA:tests of 17 abilities: ability to stand, rise from floor, get from lying to sitting, from sitting to standing, raise one's head, stand on one's heels, hop, jump, and run. For each activity, a score of 0,1, or 2 was recorded, with 0="unable to achieve independently," 1="modified method but achieves goal independently," or 2="normal- achieves goal without any assistance." Sum of these 17 scores was reported as ordinal total score, which can be transformed to a linear total score from 0(worst) to 100(best). Number of participants analyzed=195 (ambulatory participants with a baseline value).			
Units: units on a scale			
arithmetic mean	20.73		
standard deviation	± 8.513	-	
Performance Upper Limb (PUL) Total Score			
PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into shoulder level (4 items), elbow level (9 items), and distal level (8 items) dimensions. Scoring options per item may vary from 0-1 and 0-6, with higher values corresponding to better performance. Each dimension was scored separately with a maximum score of 16 for shoulder level, 34 for elbow level, and 24 for distal level. Total score was calculated by adding the 3 level scores (maximum global score of 74). Number of participants analyzed for this baseline measure are 210.			
Units: units on a scale			
arithmetic mean	68.7		
standard deviation	± 4.61	-	
Percent Predicted Forced Vital Capacity (FVC)			
FVC is a standard pulmonary function test. FVC was defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Percent predicted FVC (in %) = [(observed FVC)/(predicted FVC)]*100. Number of participants analyzed for this baseline measure are 210.			
Units: percent predicted FVC			
arithmetic mean	59.42		
standard deviation	± 13.843	-	
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1)			
FEV1 is a standard pulmonary function test. FEV1 was defined as the volume of air that can forcibly be blown out in 1 second, after full inspiration in the upright position, measured in liters. Percent predicted FEV1 (in %) = [(observed FEV1)/(predicted FEV1)]*100. Number of participants analyzed for this baseline measure are 209.			
Units: percent predicted FEV1			
arithmetic mean	53.76		
standard deviation	± 12.870	-	
Peak Expiratory Flow (PEF)			
PEF was defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. Number of participants analyzed for this baseline measure are 213.			
Units: liters/second (L/sec)			
arithmetic mean	3.36		
standard deviation	± 1.055	-	
Peak Cough Flow (PCF)			
PCF measures an individual's maximum speed of expiration during cough. Number of participants			

analyzed for this baseline measure are 194.			
Units: L/sec			
arithmetic mean	3.30		
standard deviation	± 1.139	-	
Pediatric Outcomes Data Collection Instrument (PODCI) Transfers/Basic Mobility Score			
PODCI includes a Global Functioning Scale and 5 core scales: Upper Extremity & Physical Function,Transfer/Basic Mobility, Sports/Physical Functioning, Pain/Comfort,and Happiness. Following PODCI domains were prespecified in protocol for analysis:Transfers/Basic Mobility domain assesses difficulty experienced in performing routine motor activities in daily life. Each domain was scored from 0 (poor outcome/worse health) to 100 (the highest level of functioning & least pain). Number of participants analyzed for this baseline measure are 216.			
Units: units on a scale			
arithmetic mean	74.6		
standard deviation	± 23.66	-	
Systolic blood pressure			
Number of participants analyzed for this baseline measure are 217.			
Units: millimeters of mercury (mm Hg)			
arithmetic mean	106.3		
standard deviation	± 10.72	-	
Diastolic blood pressure			
Number of participants analyzed for this baseline measure are 217.			
Units: mm Hg			
arithmetic mean	68.6		
standard deviation	± 11.01	-	
Pulse Rate			
Number of participants analyzed for this baseline measure are 217.			
Units: beats/minute			
arithmetic mean	97.0		
standard deviation	± 13.31	-	
Body Temperature			
Number of participants analyzed for this baseline measure are 217.			
Units: degrees centigrade			
arithmetic mean	36.47		
standard deviation	± 0.453	-	

End points

End points reporting groups

Reporting group title	Ataluren

Reporting group description:

Participants received ataluren suspension orally 3 times a day (TID), 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for up to 144 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:

An adverse event (AE): any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severity of AEs: graded per Common Terminology Criteria for AEs (CTCAE), Version 3.0 as Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (death). Drug-related AEs: AEs with possible, probable, unlikely relationship, or unrelated to study drug. Serious AEs (SAEs): death, a life-threatening AE, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that required medical intervention. TEAE: an AE that occurred from first dose of study drug in this study to 6 weeks after last dose. A summary of other non-serious AEs and all SAEs, regardless of causality is located in Reported AE section. As Treated (AT) population: all participants who received at least 1 dose of ataluren treatment in this study.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 6 weeks post-treatment (Week 150)

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: Endpoint is safety in nature

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: participants				
Any AEs	202			
SAEs	24			
Drug-Related AEs	44			
AEs Leading to Withdrawal From Study	1			
Mild AEs	87			
Moderate AEs	71			
Severe AEs	42			
Life-threatening AEs	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormalities in Clinical Laboratory

Parameters

End point title	Number of Participants With Abnormalities in Clinical Laboratory Parameters[2]

End point description:

Abnormalities in laboratory variables as pre-defined in protocol for safety-monitoring were: Hepatic (Serum alanine aminotransferase [ALT]: increase of greater than [>] 150 units/liter [U/L] with stable or decrease of creatinine kinese [CK]; Serum glutamyl amino transferase [GGT] [U/L]: Grade 2 [>2.5 - 5.0 * upper limit of normal {ULN}]), renal (Serum cystatin C miiligrams/liter [mg/L] >1.33 - 2.00 mg/L; Serum blood urea nitrogen [UREAN] [millimoles/liter {mmol/L}] greater than or equal to [≥]1.5 - 3.0 * ULN; Urine occult blood: 2+ [Small], 3+ [Moderate], 4+ [Large]), and electrolytes (Serum sodium: low [mmol/L], Grade 3-4 [less than {<}130 mmol/L]; serum potassium: high [mmol/L], Grade 3-4 [>6.0 mmol/L]; and Serum bicarbonate [mmol/L]: Grade 2 [<16 - 11 mmol/L]). AT population included all participants who received at least 1 dose of ataluren treatment in this extension study.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 6 weeks post-treatment (Week 150)

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: Endpoint is safety in nature

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: participants	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 6MWD at Week 144

End point title	Change From Baseline in 6MWD at Week 144

End point description:

The 6MWD test was performed in a 30 meters long flat corridor, where the participant was instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Ambulation was assessed via the 6MWD test following standardized procedures by measuring the 6MWD in meters. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWD test. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline 6MWD value at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: meters				
arithmetic mean (standard deviation)	-98.18 (± 86.604)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time to Stand From Supine Position at Week 144

End point title	Change From Baseline in Time to Stand From Supine Position at Week 144

End point description:

If the time taken to perform this test exceeded 30 seconds or if a participant could not perform this test due to disease progression, a value of 30 seconds was used. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: seconds				
arithmetic mean (standard deviation)	5.22 (± 5.104)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time to Walk/Run 10 Meters at Week 144

End point title	Change From Baseline in Time to Walk/Run 10 Meters at Week 144

End point description:

If the time taken to perform this test exceeded 30 seconds or if a participant could not perform this test due to disease progression, a value of 30 seconds was used. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:
Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: seconds				
arithmetic mean (standard deviation)	2.29 (± 1.991)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time to Climb 4 Stairs at Week 144

End point title	Change From Baseline in Time to Climb 4 Stairs at Week 144

End point description:

If the time taken to perform this test exceeded 30 seconds or if a participant could not perform this test due to disease progression, a value of 30 seconds was used. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:
Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: seconds				
arithmetic mean (standard deviation)	4.01 (± 7.260)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time to Descend 4 Stairs at Week 144

End point title	Change From Baseline in Time to Descend 4 Stairs at Week 144

End point description:

If the time taken to perform this test exceeded 30 seconds or if a participant could not perform this test due to disease progression, a value of 30 seconds was used. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at

specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: seconds				
arithmetic mean (standard deviation)	2.45 (± 5.853)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physical Function Total Score as Measured by NSAA at Week 144

End point title	Change From Baseline in Physical Function Total Score as Measured by NSAA at Week 144

End point description:

NSAA comprised tests for 17 abilities of a participant, such as ability to stand, rise from floor, get from lying to sitting, get from sitting to standing, raise one’s head, stand on one’s heels, hop, jump, and run. For each activity, a score of 0, 1, or 2 was recorded, with 0 = “unable to achieve independently,” 1 = “modified method but achieves goal independently,” or 2 = “normal- achieves goal without any assistance.” Sum of these scores (except for 'raise one's head' activity score) was reported as the ordinal total score, which was transformed to a linear total score ranging from 0 (worst) to 100 (best). Participants with confirmed loss of ambulation at a particular visit were assigned a score of 0. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: units on a scale				
arithmetic mean (standard deviation)	-7.95 (± 5.611)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PUL Total Score at Week 144

End point title	Change From Baseline in PUL Total Score at Week 144

End point description:

The PUL was used to assess motor performance of the upper limb. The PUL scale includes 22 items; an entry item defining the starting functional level, and 21 items subdivided into shoulder level (4 items), elbow level (9 items), and distal level (8 items) dimensions. Scoring options per item may not be uniform and may vary from 0-1 and 0-6, according to the performance, with higher values corresponding to better performance. Each dimension was scored separately with a maximum score of 16 for shoulder level, 34 for elbow level, and 24 for distal level. Total score was calculated by adding the 3 level scores (maximum global score of 74). AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: units on a scale				
arithmetic mean (standard deviation)	-4.0 (± 7.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Predicted FVC as Measured by Spirometry at Week 144

End point title	Change From Baseline in Percent Predicted FVC as Measured by Spirometry at Week 144

End point description:

FVC is a standard pulmonary function test. FVC was defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Percent predicted FVC (in %) = [(observed FVC)/(predicted FVC)]*100. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: percent predicted FVC				
arithmetic mean (standard deviation)	3.51 (± 14.253)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Predicted FEV1 as Measured by Spirometry at Week 144

End point title	Change From Baseline in Percent Predicted FEV1 as Measured by Spirometry at Week 144

End point description:

FEV1 is a standard pulmonary function test. FEV1 was defined as the volume of air that can forcibly be blown out in 1 second, after full inspiration in the upright position, measured in liters. Percent predicted FEV1 (in %) = [(observed FEV1)/(predicted FEV1)]*100. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: percent predicted FEV1				
arithmetic mean (standard deviation)	1.40 (± 15.319)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PEF as Measured by Spirometry at Week 144

End point title	Change From Baseline in PEF as Measured by Spirometry at Week 144

End point description:

PEF was defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: L/sec				
arithmetic mean (standard deviation)	0.23 (± 1.099)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PCF as Measured by Spirometry at Week 144

End point title	Change From Baseline in PCF as Measured by Spirometry at Week 144

End point description:

PCF measures an individual's maximum speed of expiration during cough. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: L/sec				
arithmetic mean (standard deviation)	0.53 (± 1.281)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PODCI Transfers/Basic Mobility Score at Week 144

End point title	Change From Baseline in PODCI Transfers/Basic Mobility Score at Week 144

End point description:

Changes in health-related quality of life (HRQL) were measured via the PODCI questionnaire that has been shown to correlate with disease progression and clinical outcome measures in DMD. PODCI includes a Global Functioning Scale and 5 core scales: Upper Extremity and Physical Function,

Transfer/Basic Mobility, Sports/Physical Functioning, Pain/Comfort,and Happiness. The following PODCI domain was prespecified in the protocol for analysis:Transfers/Basic Mobility domain assesses difficulty experienced in performing routine motor activities in daily life. Each domain was scored from 0 to 100, with 0 representing a poor outcome/worse health, while 100 representing the highest level of functioning and least pain. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: units on a scale				
arithmetic mean (standard deviation)	-29.3 (± 25.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change From Baseline in Activities of Daily Living and Disease Status at Week 144, as Assessed by a Standardized Survey Administered by Site Personnel

End point title	Number of Participants With Change From Baseline in Activities of Daily Living and Disease Status at Week 144, as Assessed by a Standardized Survey Administered by Site Personnel

End point description:

Changes in activities of daily living and disease symptoms were captured via a DMD-specific survey administered by Site personnel. At screening/baseline, participant and/or parent/caregiver were asked to identify any activities of daily living or symptoms that were affected by participant's DMD. At post-baseline visit (Week 144), the same participant and/or parent/caregiver was asked to describe any changes from baseline in those activities of daily living/symptoms, within the following categories: physical functioning (PF); general energy level (GEL); cognition/school function (C/SF); emotional/social functioning (E/SF); and sleep. Changes from baseline were reported on a 5-point Likert scale: 1 (much better), 2 (slightly better), 3 (unchanged), 4 (slightly worse), or 5 (much worse). AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'n'signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: participants				
PF- Walking: Much better (n=143)	6			
PF- Walking: Slightly better (n=143)	3			
PF- Walking: Unchanged (n=143)	47			
PF- Walking: Slightly worse (n=143)	32			
PF- Walking: Much worse (n=143)	55			
PF- Climbing stairs: Much better (n=141)	6			
PF- Climbing stairs: Slightly better (n=141)	4			
PF- Climbing stairs: Unchanged (n=141)	37			
PF- Climbing stairs: Slightly worse (n=141)	29			
PF- Climbing stairs: Much worse (n=141)	65			
PF- Upper Extremity Activity: Much better (n=119)	5			
PF-Upper Extremity Activity:Slightly better(n=119)	6			
PF- Upper Extremity Activity: Unchanged (n=119)	75			
PF- Upper Extremity Activity:Slightly worse(n=119)	21			
PF- Upper Extremity Activity: Much worse (n=119)	12			
PF- Other: Much better (n=62)	3			
PF- Other: Slightly better (n=62)	2			
PF- Other: Unchanged (n=62)	29			
PF- Other: Slightly worse (n=62)	13			
PF- Other: Much worse (n=62)	15			
E/SF: Much better (n=134)	13			
E/SF: Slightly better (n=134)	16			
E/SF: Unchanged (n=134)	93			
E/SF: Slightly worse (n=134)	7			
E/SF: Much worse (n=134)	5			
C/SF: Much better (n=133)	9			
C/SF: Slightly better (n=133)	24			
C/SF: Unchanged (n=133)	92			
C/SF: Sightly worse (n=133)	8			
C/SF: Much worse (n=133)	0			
GEL: Much better (n=127)	8			
GEL: Slightly better (n=127)	8			
GEL: Unchanged (n=127)	82			
GEL: Slightly worse (n=127)	21			
GEL: Much worse (n=127)	8			
Sleep: Much better (n=128)	11			
Sleep: Slightly better (n=128)	11			
Sleep: Unchanged (n=128)	95			
Sleep: Slightly worse (n=128)	9			
Sleep: Much worse (n=128)	2			
Other: Much better (n=31)	2			

Other: Slightly better (n=31)	2			
Other: Unchanged (n=31)	12			
Other: Slightly worse (n=31)	8			
Other: Much worse (n=31)	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Ataluren Plasma Concentration

End point title	Ataluren Plasma Concentration

End point description:

Pre-dose ataluren plasma concentrations prior to morning ataluren administration at each clinic visit was assessed using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) method. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'n' signifies participants evaluable for this outcome measure at specified timepoints.

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: micrograms/milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Week 12 (n=210)	4.5231 (± 5.08583)			
Week 24 (n=211)	4.4817 (± 5.65883)			
Week 36 (n=205)	5.1551 (± 5.67555)			
Week 48 (n=201)	5.2221 (± 5.32846)			
Week 60 (n=191)	5.0396 (± 5.07812)			
Week 72 (n=180)	6.0677 (± 6.05912)			
Week 84 (n=171)	5.4673 (± 5.15083)			
Week 96 (n=160)	5.8870 (± 5.90954)			
Week 108 (n=133)	5.5905 (± 6.48016)			
Week 120 (n=119)	5.2406 (± 5.69648)			
Week 132 (n=94)	6.6729 (± 7.03882)			
Week 144 (n=66)	5.3898 (± 6.28487)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systolic and Diastolic Blood Pressure at Week 144

End point title	Change From Baseline in Systolic and Diastolic Blood Pressure at Week 144

End point description:

Blood pressure determination was performed with the participant in a sitting position after a 5-minute rest. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'n' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic blood pressure (n=68)	0.8 (± 11.86)			
Diastolic blood pressure (n=63)	1.3 (± 11.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulse Rate at Week 144

End point title	Change From Baseline in Pulse Rate at Week 144

End point description:

Pulse rate determination was performed with the participant in a sitting position after a 5-minute rest. AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: beats/minute				
arithmetic mean (standard deviation)	-0.9 (± 13.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Temperature at Week 144

End point title	Change From Baseline in Body Temperature at Week 144

End point description:

AT population included all participants who received at least 1 dose of ataluren treatment in this extension study. Here, 'Overall number of participants analyzed' = participants who had both baseline and post-baseline value of this parameter at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 144

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: degrees centigrade				
arithmetic mean (standard deviation)	0.05 (± 0.545)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to 6 weeks post-treatment (Week 150)

Adverse event reporting additional description:

AT population included all participants who received at least 1 dose of ataluren treatment in this extension study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

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 up to 144 weeks.

Serious adverse events	Ataluren		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 218 (11.01%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Exposure to communicable disease			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Laceration			

subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Transposition of the great vessels			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular septal defect			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intussusception			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Pneumonia aspiration			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary artery stenosis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint contracture			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendinous contracture			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Adenoiditis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			

subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic sinusitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 218 (0.46%)		
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	201 / 218 (92.20%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	48 / 218 (22.02%)		
occurrences (all)	76		
Ligament sprain			
subjects affected / exposed	19 / 218 (8.72%)		
occurrences (all)	22		
Nervous system disorders			
Headache			
subjects affected / exposed	42 / 218 (19.27%)		
occurrences (all)	116		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	56 / 218 (25.69%)		
occurrences (all)	56		
Pyrexia			
subjects affected / exposed	26 / 218 (11.93%)		
occurrences (all)	33		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	18 / 218 (8.26%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	17 / 218 (7.80%)		
occurrences (all)	22		
Nausea			
subjects affected / exposed	16 / 218 (7.34%)		
occurrences (all)	27		
Vomiting			
subjects affected / exposed	37 / 218 (16.97%)		
occurrences (all)	71		

Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 26 / 218 (11.93%) 40		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 20 / 218 (9.17%) 26		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 14 / 218 (6.42%) 20 27 / 218 (12.39%) 29 26 / 218 (11.93%) 41		
Infections and infestations Ear infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 11 / 218 (5.05%) 12 18 / 218 (8.26%) 25 23 / 218 (10.55%) 30 57 / 218 (26.15%) 99 28 / 218 (12.84%) 62		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2015	Changes to the conduct of the study included the following: • Study treatment period was extended from 96 weeks to 144 weeks. • Blood drawing requirements were updated to specify the number of tubes for blood trough PK would be 10 rather than 8 and the total blood volume drawn from screening to end of study would be 152 milliliters (mL). • Language discouraging the use of cardiac drugs for prophylactic/treatment of congestive heart failure (CHF) was removed. • Language regarding weight-based dosing assessments was simplified to specify assessments be made every 6 months. • Exempted participants who terminated from study early due to a transition to commercial ataluren from the 6-week post treatment follow-up visit. • Removed requirement for videotaping the 6MWT, timed function tests, NSAA, and PUL assessments.

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.

The study was terminated early per Sponsor decision due to commercial availability of ataluren.

Notes: