Clinical trial results:
Phase 2 Clinical Pharmacology Study to Assess Dystrophin Levels in Subjects With nmDMD Before and After Treatment with Ataluren

Summary

EudraCT number	2019-001767-67
Trial protocol	Outside EU/EEA
Global end of trial date	23 October 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-045-DMD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03648827
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	100 Corporate Court, South Plainfield, United States, NJ 07080
Public contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2020
Global end of trial reached?	Yes
Global end of trial date	23 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the change in levels of dystrophin in ambulatory participants with nonsense mutation Duchenne Muscular Dystrophy (nmDMD) after treatment with ataluren for 40 weeks using quantitative assay, such as electrochemiluminescence (ECL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

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)	20
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 21 participants were screened, one of whom did not meet eligibility criteria. The remaining 20 participants who signed the informed consent and were not screen failures comprise the Enrolled Population.

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 oral suspension 10 milligrams per kilogram (mg/kg) in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 40 weeks.

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

Dosage and administration details:

Ataluren was administered as per the dose and schedule specified in the arm description.

Number of subjects in period 1	Ataluren
Started	20
Received at least 1 dose of study drug	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Participants received ataluren oral suspension 10 milligrams per kilogram (mg/kg) in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 40 weeks.	

Reporting group values	Ataluren	Total	
Number of subjects	20	20	
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)	20	20	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	4.8		
standard deviation	± 1.77	-	
Sex: Female, Male Units: participants			
Female	0	0	
Male	20	20	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	17	17	
More than one race	1	1	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	15	15	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Ataluren

Reporting group description:

Participants received ataluren oral suspension 10 milligrams per kilogram (mg/kg) in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 40 weeks.

Primary: Percent Change From Baseline in Dystrophin Level at Week 40, as Measured by ECL

End point title	Percent Change From Baseline in Dystrophin Level at Week 40, as Measured by ECL[1]

End point description:

The percent change in dystrophin level from baseline in ambulatory nonsense mutation duchenne muscular dystrophy (nmDMD) participants after treatment with ataluren for 40 weeks was analyzed using quantitative assay (ECL).The least square (LS) mean and 90% confidence interval (CI) were analyzed from a mixed-model repeated measures (MMRM) with factors of muscle locations and visits as fixed effects, and participants as a random effect. Intent-to-treat (ITT) population included all enrolled participants with a valid assessment of dystrophin level at baseline, as measured by ECL.

End point type	Primary

End point timeframe:

Baseline, Week 40

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: Statistical analysis was not planned for this endpoint.

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percent change				
least squares mean (confidence interval 90%)	6.559 (-8.402 to 23.963)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dystrophin Level at Week 40, as Determined by Immunohistochemistry (IHC) Membrane Stain Density

End point title	Percent Change From Baseline in Dystrophin Level at Week 40, as Determined by Immunohistochemistry (IHC) Membrane Stain Density

End point description:

The percent change in dystrophin level from baseline in ambulatory nmDMD participants after 40 weeks of ataluren therapy was determined by IHC membrane stain density. The LS mean and 90% CI were analyzed from an MMRM with factors of muscle locations and visits as fixed effects, and participants as a random effect. ITT population included all enrolled participants with a valid assessment of dystrophin level at baseline, as measured by ECL.

End point type	Secondary

End point timeframe:
Baseline, Week 40

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percent change				
least squares mean (confidence interval 90%)	4.914 (-1.642 to 11.906)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 40	
Adverse event reporting additional description:	
Safety Population included all participants who received at least 1 dose of ataluren.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Participants received ataluren oral suspension 10 milligrams per kilogram (mg/kg) in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 40 weeks.	

Serious adverse events	Ataluren		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 20 (5.00%)		
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	18 / 20 (90.00%)		
Investigations			
Urine output increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Femur fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Gait inability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Abdominal pain			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Miliaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Behaviour disorder			

subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Conjunctivitis bacterial subjects affected / exposed occurrences (all) Influenza	 2 / 20 (10.00%) 3 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 		

subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Pharyngitis streptococcal subjects affected / exposed occurrences (all) Pneumonia bacterial subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 2 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2018	The changes implemented with this amendment are: - Text was added in objectives to clarify that secondary and exploratory objective assessments and endpoints will be collected after 40 weeks of ataluren treatment. An exploratory objective was added to evaluate pharmacokinetics of ataluren at 40 weeks of treatment. - Text was added in endpoints to clarify that exploratory endpoints will be collected after 40 weeks of ataluren treatment. An exploratory endpoint was added to evaluate pharmacokinetics of ataluren at Week 1 and Week 40 of ataluren of treatment. - The age of participants that will be included from the study was increased to >2 and <8 years of age from <7 years of age to increase study enrollment. - Removed that phenotypic evidence of DMD must be evident by 6 years of age. - Pharmacokinetic (PK) sampling was added for pharmacokinetic evaluation. For Visit 1, samples will be drawn pre-first study dose and 2 hours postdose, and on Visit 3 will be drawn pre-morning dose and 2 hours postdose. - Visit 2 was changed from Week 19 to Week 20. - The location of the biopsies was changed from right vastus lateralis and right tibialis anterior muscles to the biceps and gastrocnemius muscles. If the bicep muscle is considered by the investigator to be too small for a biopsy sample, the right tibialis anterior muscle may be used. - The text was revised from 9-month treatment period to a 40-week treatment period.
06 May 2019	The changes implemented with this amendment are: - Exploratory endpoints: deleted specific PK parameters. - Revised from 3 muscle biopsy samples to up to approximately 450 mg of muscle tissue (up to 4 cores per muscle); allowed sample from the right tibialis anterior muscle if obtained sample is not evaluable for analysis. - Extended screening window from 30 to 45 days; added details for assessing height/weight and physical exams, deleted details of PK analyses. - Added information on Cardiac Drugs for Cardiomyopathy Prophylaxis/Treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported