Clinical trial results:
A Phase 2a Study of Ataluren (PTC124) as an Oral Treatment for Nonsense-Mutation-Mediated Hemophilia A and B

Summary

EudraCT number	2010-020224-22
Trial protocol	FR
Global end of trial date	30 August 2011

Results information

Result version number	v1 (current)
This version publication date	13 June 2020
First version publication date	13 June 2020

Trial information

Trial identification

Sponsor protocol code	PTC124-GD-011-HEM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00947193
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2011
Global end of trial reached?	Yes
Global end of trial date	30 August 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine whether ataluren provides pharmacological effect in hemophilia type A (HA)/type B (HB) as measured by plasma factor 8 (FVIII)/factor 9 (FIX) activity.

Protection of trial subjects:

The trial was conducted in accordance with Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000), FDA GCP regulations (CFR 21 parts 50, 56, and 312), and the International Conference on Harmonisation (ICH) GCP guidance documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2009
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	Italy: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	13
EEA total number of subjects	5

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this study, participants with HA or HB due to a nonsense mutation were recruited for the study.

Pre-assignment

Screening details:

Participants requiring treatment with FVIII/FIX concentrate during 14-day ataluren treatment could continue ataluren treatment for at least 14 days following discontinuing FVIII concentrate treatment for HA and for at least 18 days following discontinuing FIX concentrate treatment for HB.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	5 mg/kg, 5 mg/kg, and 10 mg/kg Ataluren

Arm description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 5 milligrams/kilograms (mg/kg) in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	
Other name	PTC124®
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	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren

Arm description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Arm type	Experimental
Investigational medicinal product name	Ataluren
Investigational medicinal product code	
Other name	PTC124®
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	5 mg/kg, 5 mg/kg, and 10 mg/kg Ataluren	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren
Started	3	10
Received at Least 1 Dose of Study Drug	3	10
Completed	0	10
Not completed	3	0
Factor VIII >1%	1	-
Consent withdrawn by subject	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	13	13	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42		
standard deviation	± 17.3	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	13	13	

Subject analysis sets

Subject analysis set title	Ataluren Overall Study
Subject analysis set type	Full analysis

Subject analysis set description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening or 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Subject analysis set title	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Reporting group values	Ataluren Overall Study	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren	
Number of subjects	13	10	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	9	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42	43.8	
standard deviation	± 17.3	± 18.7	
Gender Categorical Units: Subjects			
Female	0	0	
Male	13	10	

End points

End points reporting groups

Reporting group title	5 mg/kg, 5 mg/kg, and 10 mg/kg Ataluren

Reporting group description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 5 milligrams/kilograms (mg/kg) in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Reporting group title	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren

Reporting group description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Subject analysis set title	Ataluren Overall Study
Subject analysis set type	Full analysis

Subject analysis set description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening or 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Subject analysis set title	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.

Primary: Number of Participants With a Plasma FVIII/FIX Activity Response at Day 14

End point title	Number of Participants With a Plasma FVIII/FIX Activity Response at Day 14[1]

End point description:

A plasma FVIII/FIX activity response was defined as an end-of-treatment (Day 14) activity of ≥1%. Population included all enrolled participants who received at least 1 dose of study drug and completed the study.

End point type	Primary

End point timeframe:

Baseline up to Day 14

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: This type of statistical analysis is not applicable for this endpoint.

End point values	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Change From Baseline in Plasma Anti-FVIII/FIX Inhibitor Titers at Day 14

End point title	Number of Participants With a Change From Baseline in Plasma Anti-FVIII/FIX Inhibitor Titers at Day 14

End point description:

To assess the change from Baseline in plasma anti-FVIII/FIX inhibitor titers, it was determined if any potential antibodies were neutralizing using the Bethesda assay. The Bethesda assay demonstrates antibodies that are neutralizing by quantifying residual FVIII/FIX activity in normal plasma after serial dilutions with participant plasma. For this assay, the neutralizing antibody threshold value was 0.6 Bethesda units (BU). Population included all enrolled participants who received at least 1 dose of study drug and completed the study.

End point type	Secondary

End point timeframe:

Baseline and Day 14

End point values	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs) by Severity and Relationship to Study Drug

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (SAEs) by Severity and Relationship to Study Drug

End point description:

The relationship of TEAEs and SAEs to the study drugs was assessed as: probable related, possible related, unlikely related, and unrelated. The severity of TEAEs were graded using the Common Terminology Criteria for Adverse Events, Version 3.0, as: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal). A summary of other non-serious adverse events (AEs) and all serious AEs, regardless of causality is located in Reported AE section. Population included all enrolled participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Ataluren Overall Study			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: participants				
TEAEs	8			
TEAEs Related to Study Drug	2			
Severe TEAEs	0			
SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Clinically Meaningful Abnormal Adrenal assays, Biochemistry, and Urinalysis Parameters

End point title	Number of Participants With a Clinically Meaningful Abnormal Adrenal assays, Biochemistry, and Urinalysis Parameters

End point description:

The Investigator used his/her judgment in determining whether an abnormality was clinically significant, diagnostic evaluation was warranted, and potential interruption of ataluren was appropriate. Life-threatening (Grade 4) or severe (Grade 3) laboratory abnormalities were considered dose-limiting, although recurrent or persistent moderate (Grade 2) events were also considered dose-limiting in certain circumstances. Values considered abnormal included -Adrenal: Plasma adrenocorticotropic hormone >ULN (and cortisol within normal limits); and -Renal: serum creatinine Grade 1 (>ULN–1.5*ULN) and Serum blood urea nitrogen ≥1.5–3.0*ULN. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Population included all enrolled participants who received at least 1 dose of study drug and had evaluable parameter data.

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Ataluren Overall Study			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: participants				
Biochemistry Assays	0			
Adrenal Assays	0			
Urinalysis	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Clinically Meaningful Hematology Parameters

End point title	Number of Participants With a Clinically Meaningful Hematology Parameters

End point description:

The Investigator used his/her judgment in determining whether an abnormality was clinically significant, diagnostic evaluation was warranted, and potential interruption of ataluren was appropriate. Life-threatening (Grade 4) or severe (Grade 3) laboratory abnormalities were considered dose-limiting, although recurrent or persistent moderate (Grade 2) events were also considered dose-limiting in certain circumstances. Values considered abnormal included Serum total bilirubin Grade 2 (>1.5-3.0*upper limit of normal [ULN]) and Serum alanine aminotransferase, Serum aspartate aminotransferase, and Serum gamma glutamyl transferase Grade 2 (>2.5-3.0*ULN). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Population included all enrolled participants who received at least 1 dose of study drug and had

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Ataluren Overall Study			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance With Ataluren Administration

End point title	Compliance With Ataluren Administration

End point description:

Ataluren compliance as assessed by quantification of used and unused drug. Data were not collected or analyzed for this measure because participants were terminated early from the study. Population included all enrolled participants who received at least 1 dose of study drug, completed the study, and had evaluable compliance with ataluren administration data.

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Ataluren Overall Study			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: Number				

Notes:

[2] - Data were not collected/analyzed because participants were terminated early from study.

Statistical analyses

No statistical analyses for this end point

Secondary: Ataluren Plasma Exposure

End point title	Ataluren Plasma Exposure

End point description:

The ataluren plasma concentrations before and 2 hours after the first morning dose at end of treatment was measured. Population included all enrolled participants who received at least 1 dose of study drug, completed the study, and had evaluable plasma data.

End point type	Secondary

End point timeframe:

Day 10 (pre-dose) and Day 14 (post-dose)

End point values	10 mg/kg, 10 mg/kg, and 20 mg/kg Ataluren			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: microgram/milliliters (µg/mL)				
median (full range (min-max))				
Pre-Dose	14.7 (5.94 to 28.7)			
Post-Dose	6.66 (1.04 to 28.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Bleeding Episodes

End point title	Occurrence of Bleeding Episodes

End point description:

Frequency, timing, anatomic location, and severity of any bleeding episodes were recorded. A summary of serious and all other non-serious adverse events, regardless of causality, is located in the Reported Adverse Events module. Population included all enrolled participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Ataluren Overall Study			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 28	
Adverse event reporting additional description:	
Adverse event data were collected from all enrolled participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Ataluren Overall Study
Reporting group description:	
Ataluren was provided as a vanilla-flavored powder to be mixed with water or milk. Ataluren was taken 3 times per day, with dosing based on the participant's body weight. The dose level for ataluren was 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening or 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 14 days, followed by an interval of 14 days without treatment.	

Serious adverse events	Ataluren Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Ataluren Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dyspepia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2009	-Clarification that the study would only be enrolling adults who were able to provide consent. -Clarification that participants would be provided a stipend for participation in the study. -Clarification that only the participants would be given instruction on study drug preparation. -Clarification that the screening period would be extended to -14 to -1 days. -Addition of vital signs measurements. -Addition of height and weight measurements. -Clarification that participants' FVIII/FIX activity level should be checked approximately 5 to 7 days after the last FVIII/FIX concentrate infusion during the pretreatment and treatment periods. -Clarification that bleeding episodes would be recorded in a patient diary. -Clarification that FVIII/FIX activity assessment would be performed using a clotting assay. In addition, a chromogenic assay and a thrombin generation assay would be performed. -Clarification that ataluren plasma samples would be collected at Visit 9 (Day 14 of Cycle 2).
09 April 2010	-The amendment reduced the number of clinic visits by reducing the number of cycles of ataluren administration from 2 to 1. In addition, the amendment specified that the dose level of ataluren for the single cycle would be 10 mg/kg (in the morning), 10 mg/kg (at midday), and 20 mg/kg (in the evening). The rationale for eliminating 1 cycle of ataluren administration is to simplify the study and thus enhance the ability to accumulate sufficient data to address the primary objective of determining the pharmacologic effect of ataluren on plasma FVIII/FIX activity. The rationale for changing to a single dose level from those previously proposed is to accommodate the amended 1-cycle study design and to reconsider dosing in the context of data from other nonsense mutation genetic disorders. Previously, this hemophilia study was to assess 2 dose levels: a low dose level of 5, 5, 10 mg/kg in the first cycle and a high dose level of 20, 20, 40 mg/kg in the second cycle. For the revised protocol, a single intermediate dose level of 10, 10, 20 mg/kg will be assessed. The change of dose level is supported by knowledge that this dose level has shown pharmacodynamic activity and safety in participants with nonsense mutation cystic fibrosis (nmCF) receiving ataluren over periods of 2 weeks to 12 weeks and that the 10-, 10-, 20-mg/kg dose level is being studied in a Phase 3 study evaluating 48 weeks of ataluren treatment in nmCF.

09 April 2010	Amendment Dated April 09, 2010 Continued: The change in dose level is also supported by results from a recently completed Phase 2b study involving 48 weeks of study drug therapy in 174 participants (age range 5 to 20 years) with nonsense mutation Duchenne muscular dystrophy (nmDMD). Participants in this study were randomized to ataluren at the 20-, 20-, 40-mg/kg dose level (n=60), to ataluren at the 10-, 10-, 20-mg/kg dose level (n=57), or to placebo (n=57). The study indicated that ataluren was well tolerated at both the 20-, 20-, 40-mg/kg and 10-, 10-, 20-mg/kg dose levels. Preliminary analyses indicate that participants receiving the 10-, 10-, 20-mg/kg dose level of ataluren experienced better outcomes on measures of efficacy than participants receiving the 20-, 20-, 40-mg/kg/day dose level of ataluren or than participants receiving placebo. -The amendment allowed participants who needed treatment of a bleeding episode with FVIII/FIX concentrates to continue with ataluren administration. This was allowed through 2 bleeding episodes. This increases the likelihood that participants who have enrolled in the study will be able to complete the study and provide further activity and safety data with ataluren.
28 July 2010	-Inclusion criteria were updated to indicate that gene sequencing blood sample for reconfirmation was not needed if the participant's initial gene sequencing was performed at the reference lab being used for this study. -This version provided updated information on concomitant study medication use involving nephrotoxic intravenous antibiotics and importance for the participant to remain hydrated during the course of the study. This update was based on recent information from the Phase 3 cystic fibrosis clinical trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported