Clinical trial results:
A Phase 2 Study of Ataluren (PTC124®) as an Oral Treatment for Nonsense Mutation Methylmalonic Acidemia

Summary

EudraCT number	2009-016654-41
Trial protocol	FR GB IT BE
Global end of trial date	03 November 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-012-MMA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01141075
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, Inc., +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	10 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2011
Global end of trial reached?	Yes
Global end of trial date	03 November 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 treatment with ataluren reduces plasma methylmalonic acid (MMacid) levels.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2010
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	Belgium: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	11
EEA total number of subjects	9

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)	5
Adolescents (12-17 years)	6
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants must have been ≥2 years of age with MMacid of the mitochondrial enzyme methylmalonyl-CoA mutase gene, cobalamin A (cblA), or cobalamin B (cblB) type due to a nonsense mutation in the relevant gene as documented by genotyping.

Pre-assignment

Screening details:

This study was suspended on 27 September 2011 and was terminated on 22 April 2014 due to low enrollment and unclear pharmacologic effect in available pharmacodynamic data (not due to any safety concerns).

Period 1

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

Arms

Arm title	Ataluren

Arm description:

Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 milligrams/kilograms (mg/kg) (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.

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
Started	11
Received at Least 1 Dose of Study Drug	11
Completed	11

Period 2

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

Arms

Arm title	Ataluren

Arm description:

Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 mg/kg (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.

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
Started	11
Received at Least 1 Dose of Study Drug	11
Completed	11

Baseline characteristics

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 milligrams/kilograms (mg/kg) (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.	

Reporting group values	Ataluren	Total	
Number of subjects	11	11	
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)	5	5	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	12		
standard deviation	± 7.8	-	
Sex: Female, Male			
Units: Subjects			
Female	8	8	
Male	3	3	

End points

End points reporting groups

Reporting group title	Ataluren

Reporting group description:

Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 milligrams/kilograms (mg/kg) (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.

Reporting group title	Ataluren

Reporting group description:

Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 mg/kg (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.

Primary: Plasma Methylmalonic Acid (MMacid) Levels

End point title	Plasma Methylmalonic Acid (MMacid) Levels[1]

End point description:

Normal plasma MMacid level is <0.27 micromole/liters (umol/L). Plasma samples for MMacid levels were collected after a 2- to 4-hour fast. Plasma MMacid levels were measured by a standard gas chromatography/mass spectroscopy (GC/MS) stable-isotope dilution method. Individual participant values in plasma MMacid levels at Baseline and end-to-treatment (Day 28 and Day 29 [last day of dosing]) in each cycle were recorded. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline and Day 28 and Day 29 (last day of dosing) of Cycles 1 and 2

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	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: umol/L				
median (full range (min-max))				
Baseline of Cycle 1	153.7 (15.5 to 971.5)			
Day 28 of Cycle 1	160.3 (20.5 to 1163.3)			
Day 29 of Cycle 1	175.9 (20.4 to 1432.9)			
Baseline of Cycle 2	196.5 (29.3 to 933.1)			
Day 28 of Cycle 2	280.9 (22.8 to 1083.3)			
Day 29 of Cycle 2	188.1 (20.7 to 1390.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary MMacid Levels

End point title	Urinary MMacid Levels

End point description:

The normal urinary MMacid level is <4 millimole/mole (mmol/mol) creatinine. Urinary samples for MMacid levels were collected after a 2- to 4-hour fast. Urinary MMacid levels were measured by a standard GC/MS stable-isotope dilution method. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and Day 28 and Day 29 (last day of dosing) of Cycles 1 and 2

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mmol/mol creatinine				
median (full range (min-max))				
Baseline of Cycle 1	1870.8 (84.9 to 10875.7)			
Day 28 of Cycle 1	1953.0 (100.9 to 12768.5)			
Day 29 of Cycle 1	1364.6 (173.2 to 31412.4)			
Baseline of Cycle 2	1577.7 (241.8 to 16603.9)			
Day 28 of Cycle 2	1479.1 (162.6 to 8914.4)			
Day 29 of Cycle 2	1588.3 (150.1 to 14063.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Propionylcarnitine Levels

End point title	Plasma Propionylcarnitine Levels

End point description:

Plasma samples for propionylcarnitine levels were evaluated to detect disease activity. The level of propionylcarnitine was measured using gas chromatography and liquid chromatography with tandem mass spectroscopy (LC-MS-MS). An increase in propionylcarnitine values indicates greater disease

activity. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and Day 28 and Day 29 (last day of dosing) of Cycles 1 and 2

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: umol/L				
median (full range (min-max))				
Baseline of Cycle 1	7.5 (1.8 to 39.1)			
Day 28 of Cycle 1	6.9 (2.2 to 17.6)			
Day 29 of Cycle 1	4.3 (1.9 to 16.8)			
Baseline of Cycle 2	6.6 (1.0 to 33.9)			
Day 28 of Cycle 2	5.5 (0.9 to 19.6)			
Day 29 of Cycle 2	4.5 (0.4 to 17.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Urine Methylcitric Acid Levels

End point title	Urine Methylcitric Acid Levels

End point description:

Urine methylcitric acid levels were evaluated to detect disease activity. An increase in methylcitric acid values indicates greater disease activity. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and Day 28 and Day 29 (last day of dosing) of Cycles 1 and 2

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mmol/mol creatinine				
median (full range (min-max))				
Baseline of Cycle 1	48.1 (10.2 to 309.5)			
Day 28 of Cycle 1	124.2 (12.0 to 380.3)			

Day 29 of Cycle 1	83.2 (17.3 to 498.4)			
Baseline of Cycle 2	84.9 (14.2 to 211.0)			
Day 28 of Cycle 2	72.3 (35.7 to 243.5)			
Day 29 of Cycle 2	65.1 (30.3 to 201.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the Investigator on a scale of mild, moderate and severe, with severe as an AE that prevents usual activities. Relationship of AE to treatment was determined by the Investigator. Serious AEs include death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent the previously listed serious outcomes. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 112 (end of study follow-up)

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
Any AE	10			
Severe AE	0			
Treatment-related AE	3			
Serious AE	0			
AE leading to discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Potentially Clinically Significant Laboratory (Hematology and Biochemistry) Abnormal Results

End point title	Number of Participants with Potentially Clinically Significant Laboratory (Hematology and Biochemistry) Abnormal Results

End point description:

Results graded according to Common Terminology Criteria for Adverse Events (CTCAE) severity grade (Grade [G]1 [mild], G2 [moderate], G3 [severe], G4 [life-threatening], or G5 [fatal]). Life-threatening (G4) or severe (G3) laboratory abnormalities were considered clinically significant. Recurrent/persistent moderate (G2) abnormalities were also considered clinically significant in certain circumstances. Hematology: white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. Biochemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (direct and indirect), aspartate aminotransferase, alanine aminotransferase, glutamyl transferase, creatine kinase, lactate dehydrogenase, alkaline phosphatase, total cholesterol, and triglycerides. Population: randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 112 (end of study follow-up)

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
With at least 1 hematology abnormality	0			
With at least 1 biochemistry abnormality	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Metabolic Decompensation Episode

End point title	Number of Participants with a Metabolic Decompensation Episode

End point description:

A metabolic decompensation episode is characterized by vomiting, hypotonia, and alteration of consciousness associated with metabolic acidosis and hyperammonemia. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 112 (end of study follow-up)

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Compliant with Study Treatment

End point title	Number of Participants Compliant with Study Treatment

End point description:

For each participant, compliance was described in terms of the proportion of drug actually taken relative to the amount that should have been taken during the time the participant was on study (both Cycle 1 and Cycle 2). Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 29 of Cycles 1 and 2

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
Received all doses of study drug	11			
Received at least 1 different dose than planned	4			

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 on Days 1 and 28 of Cycles 1 and 2 were measured. Validated quantitative methods employing HPLC-MS-MS were used to determine plasma concentrations of unchanged ataluren. Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

0 (predose), 1, 2, 3, and 4 hours postdose of the morning dose and 0 (predose) of the midday dose on Day 0 of Cycles 1 and 2; 0 (predose), 1, 2, 3, and 4 hours postdose of the morning dose, the midday dose, and the evening dose on Day 28 of Cycles 1 and 2

End point values	Ataluren			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: microgram/milliliters (µg/mL)				
median (full range (min-max))				
Baseline of Cycle 1	6.1 (1.3 to 16.3)			

Day 28 of Cycle 1	6.6 (0.6 to 29.9)			
Baseline of Cycle 2	14.5 (3.2 to 29.2)			
Day 28 of Cycle 2	13.2 (1.8 to 44.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 112 (end of study follow-up)	
Adverse event reporting additional description:	
All randomized participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Ataluren
Reporting group description:	
Cycle 1: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 5 mg/kg (morning), 5 mg/kg (midday), and 10 mg/kg (evening); there was then an interval of 21 up to 42 days without treatment. Cycle 2: Ataluren treatment was taken 3 times per day with meals for 28 days at doses of 10 mg/kg (morning), 10 mg/kg (midday), and 20 mg/kg (evening); there was then an interval of 14 days without treatment.	

Serious adverse events	Ataluren		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)		
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			

Convulsion subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 3		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all)	 2 / 11 (18.18%) 3 4 / 11 (36.36%) 8 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 4		
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Skin and subcutaneous tissue disorders			

Skin discolouration subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Renal and urinary disorders Glomerular vascular disorder subjects affected / exposed occurrences (all) Hypercreatininaemia subjects affected / exposed occurrences (all)	 2 / 11 (18.18%) 5 2 / 11 (18.18%) 3		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Scoliosis subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 4 / 11 (36.36%) 4		
Metabolism and nutrition disorders Hypercalcaemia subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia	 1 / 11 (9.09%) 2 1 / 11 (9.09%) 1		

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2010	This amendment was to incorporate the following changes to the protocol: • Updated information on concomitant medication use involving nephrotoxic IV antibiotics and the importance of staying hydrated during the course of the study was provided, based on newly available data from Phase 3 study ataluren in cystic fibrosis. • Baseline ages for the Bayley Scale of Infant Development, the Wechsler Preschool and Primary Scale of Intelligence, and Wechsler Intelligence Scale for Children were changed for the purpose of internal consistency within the protocol. • Cognitive testing frequency was modified to only be performed at Screening. • Inclusion criteria for the gene sequencing sample drawn during screening were modified to not require the sample to be collected if there was written documentation that gene sequencing had been performed previously in the reference laboratory being used in this study. • The study drug administration was modified to include mixing with milk. • A stable regimen of antibiotics for participants normally receiving antibiotic therapy was defined. • Instruction to encourage study participants to maintain adequate hydration during the study was added. • Vital sign assessment visits were modified to reflect the Schedule of Events. • Biochemistry and urinalysis laboratory assessments were added to Day 28 of both cycles. • Urinalysis sample shipment was modified to require urine samples to be shipped at ambient conditions. • Glomerular filtration rate measurement was modified to include age-appropriate formulas based on serum creatinine and serum cystatin C. • The maximum and total blood volumes to be drawn for this study and the National Institutes of Health blood drawing guidelines were updated. • Guidelines for reporting the pregnancy of any participant at any time after the first administration of study drug and within 60 days of receipt of last administration of study drug were provided.

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.

Study terminated due to low enrollment and unclear pharmacologic effect in available pharmacodynamic data (not due to any safety concerns).

Notes: