Clinical trial results:
An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 in Patients with -Thalassemia Previously Enrolled in Study A536-04

Summary

EudraCT number	2014-001281-94
Trial protocol	IT GR
Global end of trial date	28 April 2020

Results information

Result version number	v1 (current)
This version publication date	14 May 2021
First version publication date	14 May 2021

Trial information

Trial identification

Sponsor protocol code	A536-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268409
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acceleron Pharma, Inc.
Sponsor organisation address	128 Sidney Street , Cambridge , United States, 01239
Public contact	Mark Turnak, Sr. Director Medical Affairs, Acceleron Pharma, Inc., +1 6173019516, mturnak@acceleronpharma.com
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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	18 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2020
Global end of trial reached?	Yes
Global end of trial date	28 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of ACE-536 in patients with β-thalassemia who were previously enrolled in study A536-04.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2014
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	Greece: 7
Country: Number of subjects enrolled	Italy: 44
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	51
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Consenting participants who met the Study A536-06 eligibility criteria immediately rolled over from Study A536-04 following the last luspatercept dose. These participants did not undero end of study visit in study A536-04 but instead were initiated immediately into the extension study.

Pre-assignment

Screening details:

Other than informed consent, procedures listed as part of the 28-day screening period were only applicable to participants with treatment interruption.

Period 1

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

Arms

Arm title	Overall trial
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	ACE-536
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Luspatercept was administered by subcutaneous injection at 0.2, 0.4, 0.6, 0.6, 1.0 or 1.25 mg/kg. No more than 4 injections were administered per dose. Participants received the dose level of luspatercept that they were assigned at study enter unless a dose modification was required.

Number of subjects in period 1	Overall trial
Started	51
Completed	1
Not completed	50
Physician decision	5
Death	1
Other	4
Withdrawal by participant	16
Study terminated by sponsor	19
Lost to follow-up	1
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	51	51	
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)	51	51	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.3		
full range (min-max)	22 to 62	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	29	29	

End points

End points reporting groups

Reporting group title	Overall trial
Reporting group description: -	
Subject analysis set title	Non-Transfusion Dependent Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All treated patients who are Non-Transfusion Dependent at baseline. Non-Transfusion Dependence is defined as having received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1. In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	
Subject analysis set title	Transfusion-Dependent Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All treated patients who are Non-Transfusion Dependent at baseline. Transfusion Dependence is defined as having received >= 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1.	

Primary: Hemoglobin Response

End point title	Hemoglobin Response[1]
End point description:	
Mean Hgb increase > 1.0g/dL during rolling 12 weeks	
End point type	Primary
End point timeframe:	
Any rolling 12 week interval	

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: The response rate for each dose group is reported in earlier section of EudraCT result posting, however, per protocol, no statistical testing is performed to compare the dose groups. Consequently, no p-value is reported in this section.

End point values	Non-Transfusion Dependent Population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percent				
number (confidence interval 95%)	77.8 (57.7 to 91.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion Reduction Response

End point title	Transfusion Reduction Response
End point description:	
>= 33% reduction in RBC transfusion burden over 12 weeks, compared to pre-treatment, in transfusion dependent subjects	
End point type	Secondary

End point timeframe:
First dose to last dose + 56 days

End point values	Transfusion-Dependent Population			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: percent				
number (confidence interval 95%)	95.8 (78.9 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: BSAP - End of Treatment - Percent Change from Baseline

End point title	BSAP - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of Treatment visit

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: percent				
arithmetic mean (standard deviation)	7.2 (± 20.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: CTX - End of Treatment - Percent Change from Baseline

End point title	CTX - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: percent				
arithmetic mean (standard deviation)	19.1 (± 46.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Erythropoeitin - End of Treatment- Change from Baseline

End point title	Erythropoeitin - End of Treatment- Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percent				
arithmetic mean (standard deviation)	69.27 (± 152.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reticulocytes - End of Treatment - Change from Baseline

End point title	Reticulocytes - End of Treatment - Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population	Transfusion-Dependent Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	18		
Units: percent				
arithmetic mean (standard deviation)	283.47 (± 257.66)	151.64 (± 300.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Transferrin - End of Treatment - Percent Change from Baseline

End point title	Transferrin - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population	Transfusion-Dependent Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	24		
Units: percent				
arithmetic mean (standard deviation)	10.1 (± 44.63)	261.66 (± 256.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Soluble Transferrin Receptor - End of Treatment - Percent Change from Baseline

End point title	Soluble Transferrin Receptor - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population	Transfusion-Dependent Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: percent				
arithmetic mean (standard deviation)	3.3 (± 23.42)	-2.6 (± 43.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ferritin - End of Treatment - Percent Change from Baseline

End point title	Ferritin - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population	Transfusion-Dependent Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: percent				
arithmetic mean (standard deviation)	-22.8 (± 38.65)	53 (± 76.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: nRBC Smear- End of Treatment - Change from Baseline

End point title	nRBC Smear- End of Treatment - Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit

End point values	Non-Transfusion Dependent Population	Transfusion-Dependent Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: /100WBC				
arithmetic mean (standard deviation)	20.05 (± 71.41)	-22 (± 52.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: LDH- End of Treatment - Percent Change from Baseline

End point title	LDH- End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
arithmetic mean (standard deviation)	-4 (± 27.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bilirubin - End of Treatment - Percent Change from Baseline

End point title	Bilirubin - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:
First dose to End of treatment visit.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent				
arithmetic mean (standard deviation)	-5.6 (± 30.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Indirect Bilirubin - End of Treatment - Percent Change from Baseline

End point title	Indirect Bilirubin - End of Treatment - Percent Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

First dose to End of treatment visit.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16[2]			
Units: percent				
arithmetic mean (standard deviation)	-2.4 (± 41.39)			

Notes:

[2] - -2.4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment emergent adverse events	
Adverse event reporting additional description:	
Treatment emergent adverse events related to study drug (reported >=5%)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Non-Serious Adverse Events
Reporting group description:	
Treatment emergent adverse events	

Serious adverse events	Non-Serious Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Non-Serious Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 51 (78.43%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	8		
Asthenia			

subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Injection site erythema			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Injection site pruritus			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Injection site swelling			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hypomenorrhoea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Investigations			

Blood pressure increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Intraocular pressure increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 51 (25.49%)		
occurrences (all)	13		
Paraesthesia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Migraine with aura			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Extramedullary haemopoiesis			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Erythroblastosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haemolytic anaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Toothache			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Telangiectasia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	19 / 51 (37.25%)		
occurrences (all)	19		
Musculoskeletal pain			
subjects affected / exposed	10 / 51 (19.61%)		
occurrences (all)	10		
Arthralgia			

subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	9		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
neck pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Bone infarction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Muscle contracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
spinal pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vertebral column mass			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Vitamin B12 deficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2014	• The approved International Nonproprietary Name for the investigational product was added. • Chiltern Pharmacovigilance's fax number was updated. • Exploratory objectives added were as follows: – To evaluate change in BMD by DXA – To evaluate change in the 6MWT distance in NTD participants • Clarification was added on how the pretransfusion Hgb threshold is to be used during study. • Dose titration rules were revised to allow for the dose level to be assessed on Day 1 of each cycle, clarification was provided that dose titration requires evaluation of 2 previous cycles at the same dose level, and clarification was provided on how Hgb measurements following transfusions should be used. • Study drug information was updated to add that a lyophilized powder formulation may be used in the study. • Clarification was provided that for EMH masses, MRI of the chest and abdomen should be performed. • Repeat assessment of blood pressure was added to confirm abnormal blood pressure measurements. • Clarification was provided for gonadal assessment as an optional procedure. • Serum iron studies were added to central laboratory testing
03 June 2015	The study was extended by an additional year in order to obtain longer-term safety and efficacy data. • Clarification around transfusion status was added. For participants with low transfusion burden, the goal of therapy is sustained increase in Hgb level. Over time, these participants may become TD due to underlying disease. If this occurred prior to entering this extension study, the participant was classified as TD and assessed for reduction in transfusion burden. For TD participants, the goal of therapy is reduced transfusion burden. Participants with reduced transfusions following treatment in the base study (Study A536-04) and prior to entry into the extension study were continued to be assessed for persistence of reduced transfusion burden. • The starting dose for participants with treatment interruption was changed to 0.8 mg/kg • The maximum dose titration tested on Study A536-04 was changed to 1.25 mg/kg. • For participants continuing treatment without interruption, ongoing treatment with ICT was allowed to continue without affecting eligibility. • Analysis of Hgb increase ≥ 1.0 g/dL was included to further explore the magnitude and duration of the effect. • MRI or DXA scans did not need to be repeated within a period of 3 months, unless clinically indicated. MRI for EMH masses were repeated to measure change in volume, and MRI of the spleen was repeated if there was an enlarged spleen or if clinically indicated. • ICT was allowed during the study as long as it was initiated at least 56 days prior to C1D1 (for interruption participants) or if required during the study.

23 May 2016	• The study was extended to up to 5 years of treatment in order to obtain longer-term safety and efficacy data. • The number of participants who enrolled in Study A536-04 was updated to reflect the actual number of participants enrolled. • LMW heparin for the treatment of SVT was allowed due to short-term treatment for SVT being common in this patient population. • A testing window was added to better accommodate participant scheduling. • Section 10.2.1, Prohibited Concomitant Medications and Procedures, was added for further clarification regarding prohibited medications and procedures. • Language was added to clarify timing of transfusions in relation to study drug administration. • The option to delay a participant's dose was added. • Cycle language regarding participant treatment interruption for site administrative reasons was updated to reflect study extension and allow time for the approval of amendments by sites. • A formal interim analysis of the safety and efficacy data was added to support registration filings
16 August 2016	• Language was added to better define reporting of AEs of special interest based on the Investigator's Brochure.
12 September 2017	• Follow-up was extended to 3 years after the last dose of luspatercept to increase the chance of detecting new malignancies. The schedule for post-treatment follow-up and long-term follow-up visits was defined. • Treatment discontinuation in response to Grade 3 leukocytosis was added to the dose modification rules in order to ensure treatment discontinuation for participants with WBC elevations highly suspicious for development of a new hematologic malignancy or other significant myeloproliferative disorder.
29 March 2019	• Language was updated to allow for the use of vials containing either 25 mg, 50 mg, or 75 mg of lyophilized ACE-536.

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.

N/A

Notes: