Clinical trial results:
An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Previously Enrolled in Study A536-03

Summary

EudraCT number	2014-001280-13
Trial protocol	DE
Global end of trial date	19 March 2020

Results information

Result version number	v1 (current)
This version publication date	04 April 2021
First version publication date	04 April 2021
Summary attachment (see zip file)	A536-05 synopsis (synopsis EN.pdf)

Trial information

Trial identification

Sponsor protocol code	A536-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acceleron Pharma Inc.
Sponsor organisation address	28 Sidney Street,, Cambridge, United States, 02139
Public contact	Mark Turnak , Acceleron Pharma Inc., +1 617 301 9516 , mturnak@acceleronpharma.com
Scientific contact	Mark Turnak, Sr. Director Medical Affairs , Acceleron Pharma Inc., +1 617 301 9516 , mturnak@acceleronpharma.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	19 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2020
Global end of trial reached?	Yes
Global end of trial date	19 March 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 low or intermediate-1 risk MDS who were previously enrolled in study A536-03.

Protection of trial subjects:

The trial was conducted under the principles of Good Clinical Practice, including human subject protection. No specific measures were warranted beyond the aforementioned and standard of care.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	09 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	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	17
From 65 to 84 years	54
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 75 of 116 subjects enrolled in Study A536-03 have continued on to the extension Study A536-05. Sixty-seven (89.3%) of these subjects rolled over directly into Study A536-05, and 8 (10.7%) subjects had a treatment interruption between Study A536-03 and Study A536-05 (subjects who completed the Study A536-03 EOS visit prior to C1D1).

Pre-assignment

Screening details:

Consenting subjects who met the Study A536-05 eligibility criteria immediately rolled over from Study A536-03 to Study A536-05 following the last luspatercept dose. These subjects did not undergo the Post-treatment Follow-up (PTFU) and End of Study (EOS) visit in Study A536-03 but instead were initiated immediately into the extension study A536-05.

Period 1

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

Blinding implementation details:

N/A

Arms

Arm title	ITT population

Arm description:

Luspatercept administered by subcutaneous injection (SC) at 0.5, 0.75, 1.0, 1.33, or 1.75 mg/kg once every 3 weeks

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

Dosage and administration details:

Luspatercept was administered by subcutaneous injection at 0.5, 0.75, 1.0, 1.33, or 1.75 mg/kg on C1D1. No more than 4 injections were administered per dose. Subsequent doses will be administered every 3 weeks on Day 1 of the cycle for up to 87 cycles. The last dose of luspatercept may not be administered after 87 cycles or 1825 calendar days from C1D1, whichever occurs first. Subjects received the dose level of luspatercept that they were assigned at study entry unless a dose modification was required.

Number of subjects in period 1	ITT population
Started	75
Completed	14
Not completed	61
Presence of >1% blast peripheral blood	1
Death	12
Study terminated by sponsor	22

other	12
Lost to follow-up	2
Protocol deviation	3
Withdrawal by subject	9

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	54	54	
85 years and over	4	4	
Age continuous Units: years			
arithmetic mean	70.9		
full range (min-max)	29 to 90	-	
Gender categorical Units: Subjects			
Female	50	50	
Male	25	25	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	67	67	
Not Reported	7	7	
Unknown	1	1	
Race Units: Subjects			
American Indian or Alaska Native		0	
Asian		0	
Black or African American		0	
White	75	75	
Other		0	

Subject analysis sets

Subject analysis set title	Low-Transfusion Burden
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All treated patients who are Low Transfusion Burden (LTB) at Baseline.
LTB subjects are defined as those who received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1

Subject analysis set title	High-Transfusion Burden
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All treated patients who are High-Transfusion Burden (HTB) at baseline.
HTB subjects are defined as those who required 4 or more units of RBC transfusions within 8 weeks prior to Cycle 1 Day 1 (-55 <= day <= 1)..

Subject analysis set title	Total
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least 1 dose of luspatercept.

Reporting group values	Low-Transfusion Burden	High-Transfusion Burden	Total
Number of subjects	50	25	75
Age categorical Units: Subjects			
Adults (18-64 years)	12	5	17
From 65-84 years	34	20	54
85 years and over	4	0	4
Age continuous Units: years			
arithmetic mean	71.8	69.1	70.9
full range (min-max)	30 to 90	29 to 79	29 to 90
Gender categorical Units: Subjects			
Female	18	7	25
Male	32	18	50
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	47	20	67
Not Reported	2	5	7
Unknown	1	0	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
White	50	25	75
Other	0	0	0

End points

End points reporting groups

Reporting group title	ITT population

Reporting group description:

Luspatercept administered by subcutaneous injection (SC) at 0.5, 0.75, 1.0, 1.33, or 1.75 mg/kg once every 3 weeks

Subject analysis set title	Low-Transfusion Burden
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All treated patients who are Low Transfusion Burden (LTB) at Baseline.
LTB subjects are defined as those who received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1

Subject analysis set title	High-Transfusion Burden
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All treated patients who are High-Transfusion Burden (HTB) at baseline.
HTB subjects are defined as those who required 4 or more units of RBC transfusions within 8 weeks prior to Cycle 1 Day 1 (-55 <= day <= 1)..

Subject analysis set title	Total
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least 1 dose of luspatercept.

Primary: Hemoglobin Response (ITT, LTB)

End point title	Hemoglobin Response (ITT, LTB)[1]

End point description:

Hemoglobin Response is defined as patients with all hemoglobin value from baseline during any rolling 8-week period were increased >= 1.5 g/dL in the absence of transfusion.

End point type	Primary

End point timeframe:

Rolling 8 Weeks
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

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 the EUDRACT results 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	Low-Transfusion Burden	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	25		
Units: percent				
number (confidence interval 95%)	66 (51.2 to 78.8)	66 (51.2 to 78.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in Transfusion Burden (ITT, HTB)

End point title	Reduction in Transfusion Burden (ITT, HTB)

End point description:

Change in Transfusion Burden in High Transfusion Burden Subjects
RBC Reduction ≥ 4 units or 50% Reduction during Rolling 8 Weeks

End point type	Secondary

End point timeframe:

Rolling 8 Weeks
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

End point values	High-Transfusion Burden	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: percent				
number (confidence interval 95%)	84 (59.3 to 93.2)	84 (59.3 to 93.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erythroid Response

End point title	Erythroid Response

End point description:

Defined as the proportion of subjects for whom the mean of all Hgb values from baseline during any rolling
8-week period increased ≥ 1.5 g/dL in the absence of transfusion for LTB subjects, or a reduction by ≥ 4 units or
≥ 50% of units of RBCs transfused over any rolling 8-week interval for HTB subject

End point type	Secondary

End point timeframe:

Any rolling 8 week window on treatment compared with baseline.
Rolling 8 weeks is defined as any consecutive 8 weeks

End point values	ITT population	Low-Transfusion Burden	High-Transfusion Burden	Total
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	75	50	25	75
Units: percent				
arithmetic mean (confidence interval	81.3 (77.7 to	80 (66.3 to	84 (63.9 to	81.3 (70.7 to

95%)	89.4)	90.0)	95.5)	89.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophil Response (ITT, HI-N Evaluable)

End point title	Neutrophil Response (ITT, HI-N Evaluable)

End point description:

Defined for subjects with baseline neutrophil count (absolute neutrophil count) < 1.0 x 10^9/L as subjects with a mean percentage increase ≥ 100% and an absolute mean increase > 0.5 x 10^9/L Response was defined as all records of neutrophil increase of ≥ 100% and an absolute increase of > 0.5

End point type	Secondary

End point timeframe:

During any rolling 8-week window on treatment compared with baseline.
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

End point values	ITT population			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent				
arithmetic mean (confidence interval 95%)	50 (23.0 to 77.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reticulocytes (ITT)

End point title	Reticulocytes (ITT)

End point description:

End of Treatment, % Change From Baseline,

End point type	Secondary

End point timeframe:

Baseline to end of treatment.
Baseline is the last observation on or prior to Cycle 1 Day 1.

End point values	ITT population	Total		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	47		
Units: 10 to 9th power/L				
arithmetic mean (standard deviation)	31.0 (± 67.8)	31.0 (± 67.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Direct Bilirubin

End point title	Direct Bilirubin

End point description:

End of Treatment, % Change From Baseline

End point type	Secondary

End point timeframe:

Baseline to end of treatment.
Baseline is the last observation on or prior to Cycle 1 Day 1.

End point values	ITT population			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: µmol/L				
arithmetic mean (standard deviation)	6.10 (± 23.677)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lactate Dehydrogenase

End point title	Lactate Dehydrogenase

End point description:

End of Treatment, % Change From Baseline

End point type	Secondary

End point timeframe:

Baseline to end of treatment.
Baseline is the last observation on or prior to Cycle 1 Day 1.

End point values	ITT population			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: U/L				
arithmetic mean (standard deviation)	43.78 (± 88.343)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events collected from first dose to end of study

Adverse event reporting additional description:

Non-Serious Adverse Events reported in ≥ 5% of subjects overall are shown.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	ITT Population

Reporting group description: -

Serious adverse events	ITT Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 75 (77.33%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transformation to acute myeloid leukaemia			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			

subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchial carcinoma				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukaemia monocytic				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cancer				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic stenosis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				

subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteritis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Autoinflammatory disease			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary congestion			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone contusion			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Compression fracture			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hip fracture				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	4 / 75 (5.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				

subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	4 / 75 (5.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Normal pressure hydrocephalus				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papilloedema			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcerative keratitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vitreous haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 75 (2.67%)		
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 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	7 / 75 (9.33%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	4 / 75 (5.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 75 (5.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	3 / 75 (4.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				

subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spondylitis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal osteomyelitis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Abscess				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				

subjects affected / exposed	1 / 75 (1.33%)		
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	ITT Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 75 (44.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	5		
Hot flush			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Adverse drug reaction			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site pain			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site pruritus			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site warmth			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Injection site inflammation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Platelet count increased			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Hypotonia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
White blood cell count increased	Additional description: leucocytosis		
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Splenomegaly			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Thrombocytopenia			

subjects affected / exposed occurrences (all) Thrombocytosis subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1 1 / 75 (1.33%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 75 (1.33%) 1		
Eye disorders eye oed subjects affected / exposed occurrences (all)	 1 / 75 (1.33%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 2 / 75 (2.67%) 2 1 / 75 (1.33%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 75 (1.33%) 1 1 / 75 (1.33%) 1		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 1 / 75 (1.33%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Bone pain	 4 / 75 (5.33%) 4 		

subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Bursitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2015	Addition of ability to include other QOL tools to evaluate patient outcomes. The study has been extended by an additional year in order to obtain longer-term safety and efficacy data. Increased total patient numbers due to increase in the number of patients planned to enroll into the base study A536-03. Starting does updated to 1.0 mg/kg. Updated the maximum dose titration not to exceed 1.75 mg/kg. Schedule of Events Table updated table to allow for treatment period of 24 months. Day 8 visits removed to simplify schedule to Q3W visits.
05 July 2016	Number of study centers increased to facilitate enrollment. The study has been extended to up to five years of treatment in order to obtain longer-term safety and efficacy data. Additional dose modification rule added to ensure patients are not showing signs of disease progression. Number of cycles increased to reflect study extension up to five years of treatment. Iron chelation therapy is allowed to be initiated during the study if required per standard of care.
05 July 2017	Medical Monitor information updated. Total number of patients increased to reflect addition of expansion cohort 3 to Study A536-03. Study design updated to indicate that only patients without treatment interruption for expansion cohorts 2 and 3 are eligible for the A536-05 study unless otherwise approved by sponsor. Updated additional monitoring of adverse events of special interest and extension of survival follow-up to 3 years. Additional dose modification rule added to ensure patients are not showing signs of disease progression.
06 March 2018	Synopsis Efficacy Assesments updated NTBI data not being used as part of analysis. Disease progression table added for reference, from Cheson, et al. Blood 2006.
29 March 2019	Dosage, and mode of administration 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

None reported