Clinical trial results:
A Phase 2, Open-Label, Ascending Dose Study of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)

Summary

EudraCT number	2012-002523-14
Trial protocol	DE
Global end of trial date	22 October 2018

Results information

Result version number	v1 (current)
This version publication date	06 November 2019
First version publication date	06 November 2019
Summary attachment (see zip file)	A536-03 CSR Synopsis (synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	A536-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01749514
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acceleron Pharma Inc.
Sponsor organisation address	128 Sidney Street, Cambridge, United States, 02139
Public contact	Peter G. Linde, MD, Acceleron Pharma Inc., +1 617.649.9202, plinde@acceleronpharma.com
Scientific contact	Peter G. Linde, MD, Acceleron Pharma Inc., +1 617.649.9202, plinde@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	22 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2018
Global end of trial reached?	Yes
Global end of trial date	22 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the proportion of patients who have a modified erythroid response (mHI-E), defined as a hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of red blood cell [RBC] transfusions) in non-transfusion dependent patients, or a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pretreatment in transfusion-dependent patients

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	21 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 116
Worldwide total number of subjects	116
EEA total number of subjects	116

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)	29
From 65 to 84 years	82

85 years and over	5

Subject disposition

Recruitment

Recruitment details:

27 patients were enrolled in the dose-escalation phase in 7 cohorts of up to 6 patients each, at dose levels (dl) of 0.125, 0.25, 0.5, 0.75, 1.0, 1.33 and 1.75 mg/kg for up to 5 cycles. 89 patients were enrolled in the expansion cohort with a starting dl of 1.0 mg/kg; dl was modified based on the change in Hgb or transfusion burden.

Pre-assignment

Screening details:

Patients with low or intermediate-1 risk MDS who were not receiving prior treatment with an ESA and meet the study eligibility criteria will be enrolled within 28 days of screening.

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

Are arms mutually exclusive?	Yes
Arm title	0.125 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 0.125 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	0.25 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 0.25 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	0.5 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 0.5 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	0.75 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 0.75 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	1.00 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 1.00 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	1.33 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 1.33 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	1.75 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 1.75 mg/kg subcutaneously (SC) once every 3 weeks

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Arm title	Expansion Cohort

Arm description:

Luspatercept starting dose 1.0 mg/kg subcutaneously (SC) once every 3 weeks. For each subsequent cycle in the expansion cohort (up to 5 cycles), a patient's dose level could be modified based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.75 mg/kg).

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:

Subjects received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.

Number of subjects in period 1	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)
Started	3	3	3
Completed	3	3	3
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Presence of >= 1% blasts in peripheral blood	-	-	-
Sponsor decision to allow anticancer treatment	-	-	-
Progressive Disease	-	-	-
Protocol deviation	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)
Started	6	3	6
Completed	6	2	5
Not completed	0	1	1
Consent withdrawn by subject	-	1	1
Physician decision	-	-	-
Presence of >= 1% blasts in peripheral blood	-	-	-
Sponsor decision to allow anticancer treatment	-	-	-
Progressive Disease	-	-	-

Protocol deviation	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Started	3	89
Completed	3	76
Not completed	0	13
Consent withdrawn by subject	-	-
Physician decision	-	4
Presence of >= 1% blasts in peripheral blood	-	1
Sponsor decision to allow anticancer treatment	-	1
Progressive Disease	-	2
Protocol deviation	-	1
Lack of efficacy	-	4

Baseline characteristics

Reporting groups	
Reporting group title	0.125 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.125 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.25 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.25 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.5 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.5 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.00 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.00 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.33 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.33 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	Expansion Cohort
Reporting group description:	
Luspatercept starting dose 1.0 mg/kg subcutaneously (SC) once every 3 weeks. For each subsequent cycle in the expansion cohort (up to 5 cycles), a patient's dose level could be modified based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.75 mg/kg).	

Reporting group values	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)
Number of subjects	3	3	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	1
From 65-84 years	1	2	2
85 years and over	1	0	0
Age continuous Units: years			
arithmetic mean	70.0	59.0	66.3
full range (min-max)	50 to 88	27 to 77	62 to 72

Gender categorical Units: Subjects			
Female	3	3	2
Male	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	2	3
Not Reported	0	1	0
Unknown	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
White	3	3	3
Other	0	0	0

Reporting group values	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)
Number of subjects	6	3	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	0	2
From 65-84 years	4	3	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.8	73.7	68.2
full range (min-max)	50 to 78	71 to 78	56 to 75
Gender categorical Units: Subjects			
Female	3	0	1
Male	3	3	5
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	3	5
Not Reported	0	0	1
Unknown	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Black or African American	0	0	0
White	6	3	6
Other	0	0	0

Reporting group values	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Total
Number of subjects	3	89	116
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	21	29
From 65-84 years	2	64	82
85 years and over	0	4	5
Age continuous Units: years			
arithmetic mean	63.7	71.6	
full range (min-max)	42 to 80	30 to 90	-
Gender categorical Units: Subjects			
Female	2	30	44
Male	1	59	72
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	80	105
Not Reported	0	8	10
Unknown	0	1	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
White	3	89	116
Other	0	0	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 (between Day -55 and Day 1).

In this study, Efficacy Evaluable population is the same as Intention-to-treat population.

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 (between Day -55 and Day 1).

In this study, Efficacy Evaluable population is the same as Intention-to-treat population.

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	65	51	116
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	13	29
From 65-84 years	45	37	82
85 years and over	4	1	5
Age continuous Units: years			
arithmetic mean	71.5	69.1	70.4
full range (min-max)	30 to 90	27 to 88	27 to 90
Gender categorical Units: Subjects			
Female	26	18	44
Male	39	33	72
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	62	43	105
Not Reported	2	8	10
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	65	51	116
Other	0	0	0

End points

End points reporting groups

Reporting group title	0.125 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.125 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.25 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.25 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.5 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.5 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.00 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.00 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.33 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.33 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	Expansion Cohort
Reporting group description:	
Luspatercept starting dose 1.0 mg/kg subcutaneously (SC) once every 3 weeks. For each subsequent cycle in the expansion cohort (up to 5 cycles), a patient’s dose level could be modified based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.75 mg/kg).	
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 (between Day -55 and Day 1). In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	
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 (between Day -55 and Day 1). In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	
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][2]

End point description:

Increase from baseline Hemoglobin of ≥ 1.5 g/dL for ≥ 14 days (in the absence of red blood cell [RBC] transfusions) in low transfusion burden (LTB) subjects

End point type	Primary

End point timeframe:

Hemoglobin Increase ≥ 1.5 g/dL during Rolling 2 Weeks.
Rolling 2 weeks is defined as any consecutive 2 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 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.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	2
Units: Percent				
number (confidence interval 0.95%)	0 (0.0 to 97.5)	0 (0.0 to 97.5)	66.7 (9.4 to 99.2)	100 (15.8 to 100)

End point values	Expansion Cohort	Low-Transfusion Burden	Total	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	58	65	65	
Units: Percent				
number (confidence interval 0.95%)	69.0 (55.5 to 80.5)	67.7 (54.9 to 78.8)	67.7 (54.9 to 78.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Transfusion Response (ITT,HTB)

End point title	Transfusion Response (ITT,HTB)[3]

End point description:

Reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pretreatment in high transfusion burden (HTB) subjects.

End point type	Primary

End point timeframe:

RBC Reduction ≥ 4 units or 50% Reduction during Rolling 8 Weeks

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

Notes:

[3] - 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 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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	1	3
Units: Percent				
number (confidence interval 0.95%)	50.0 (1.3 to 98.7)	50.0 (1.3 to 98.7)	33.3 (0.8 to 90.6)	33.3 (0.8 to 90.6)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	1	31
Units: Percent				
number (confidence interval 0.95%)	33.3 (0.8 to 90.6)	50.0 (11.8 to 88.2)	100 (2.5 to 100)	54.8 (36.0 to 72.7)

End point values	High-Transfusion Burden	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: Percent				
number (confidence interval 0.95%)	51.0 (36.6 to 65.2)	51.0 (36.6 to 65.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erythroid Response (LTB)

End point title	Erythroid Response (LTB)[4]

End point description:

For LTB subjects, an Hgb increase of ≥ 1.5 g/dL in the absence of transfusion.

End point type	Secondary

End point timeframe:

Mean Hemoglobin Increase ≥ 1.5 g/dL during Any Rolling 8-week Interval.
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.75 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Low-Transfusion Burden
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	58	65
Units: Percent				
number (confidence interval 0.95%)	33.3 (0.8 to 90.6)	100 (15.8 to 100)	55.2 (41.5 to 68.3)	53.8 (41.0 to 66.3)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: Percent				
number (confidence interval 0.95%)	53.8 (41.0 to 66.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Erythroid Response (HTB)

End point title	Erythroid Response (HTB)[5]

End point description:

RBC Reduction ≥ 4 units or 50% Reduction during rolling 8 weeks

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 during the study

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.125 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	3
Units: Percent				
number (confidence interval 0.95%)	50.0 (1.3 to	33.3 (0.8 to	33.3 (0.8 to	33.3 (0.8 to

	98.7)	90.6)	90.6)	90.6)

End point values	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	High-Transfusion Burden
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	1	31	51
Units: Percent				
number (confidence interval 0.95%)	50.0 (11.8 to 88.2)	100 (2.5 to 100)	51.6 (33.1 to 69.8)	47.1 (32.9 to 61.5)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Percent				
number (confidence interval 0.95%)	47.1 (32.9 to 61.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Erythroid Response (ITT)

End point title	Erythroid Response (ITT)[6]

End point description:

Proportion of subjects who had all Hgb value increases of ≥ 1.5 g/dL for LTB subjects or a reduction by ≥ 4 units of RBC transfusion for HTB subjects.

End point type	Secondary

End point timeframe:

From baseline during any rolling 8-week window in the absence of transfusion for LTB subjects.
Over any rolling 8-week window for HTB subjects.
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.125 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	3
Units: Percent				
arithmetic mean (confidence interval	33.3 (0.8 to	33.3 (0.8 to	33.3 (4.3 to	33.3 (0.8 to

0.95%)	90.6)	90.6)	77.7)	90.6)

End point values	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	3	89	116
Units: Percent				
arithmetic mean (confidence interval 0.95%)	50.0 (11.8 to 88.2)	100 (29.2 to 100)	53.9 (43.0 to 64.6)	50.9 (41.4 to 60.3)

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)[7]

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 × 10 ^9/L in any rolling 8-week interval.

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.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	20	27	
Units: Percent				
arithmetic mean (confidence interval 0.95%)	0 (0.0 to 97.5)	0 (0.0 to 33.6)	0 (0.0 to 30.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Ferritin (ITT)

End point title	Serum Ferritin (ITT)
End point description: Mean Percentage Change from Baseline in Serum Ferritin	
End point type	Secondary
End point timeframe: First dose to end of treatment	

End point values	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	6
Units: Percentage				
arithmetic mean (standard deviation)	-9.5 (± 23.7)	43.8 (± 11.2)	46.9 (± 111.9)	-0.7 (± 11.5)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	3	89
Units: Percentage				
arithmetic mean (standard deviation)	23.5 (± 30.3)	-0.2 (± 24.0)	-9.7 (± 15.5)	0.7 (± 35.9)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	116			
Units: Percentage				
arithmetic mean (standard deviation)	2.9 (± 37.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Erythropoietin (Safety Population)

End point title	Erythropoietin (Safety Population)
End point description: Percentage change From baseline to end of treatment. Safety Population is defined as all subjects who received at least 1 dose of luspatercept. This population was used for all safety analyses.	
End point type	Secondary

End point timeframe:

First dose to End of Treatment

End point values	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	5
Units: IU/L				
arithmetic mean (standard deviation)	144.48 (± 232.336)	110.51 (± 85.751)	122.85 (± 163.500)	1.81 (± 48.208)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	5	2	84
Units: IU/L				
arithmetic mean (standard deviation)	749.10 (± 902.000)	146.49 (± 160.087)	29.07 (± 80.426)	238.85 (± 974.226)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	106			
Units: IU/L				
arithmetic mean (standard deviation)	220.49 (± 877.537)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reticulocytes (Safety Population)

End point title	Reticulocytes (Safety Population)

End point description:

End of Treatment, % Change From Baseline,
Safety Population is defined as all subjects who received at least 1 dose of luspatercept. This population was used for all safety analyses.

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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	2	5
Units: 10 to 9th power/L				
arithmetic mean (standard deviation)	110.82 (± 127.489)	8.10 (± 0)	79.77 (± 45.816)	28.29 (± 28.434)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	74
Units: 10 to 9th power/L				
arithmetic mean (standard deviation)	76.16 (± 54.003)	0.45 (± 19.770)	84.06 (± 108.298)	41.37 (± 73.445)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: 10 to 9th power/L				
arithmetic mean (standard deviation)	44.1 (± 72.303)			

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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	1	4
Units: µmol/L				
arithmetic mean (standard deviation)	-18.45 (± 6.569)	12.38 (± 38.465)	2.33 (± 0)	7.22 (± 20.592)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	1	64
Units: µmol/L				
arithmetic mean (standard deviation)	-5.00 (± 0)	-7.41 (± 12.830)	6.78 (± 0)	-0.50 (± 27.541)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: µmol/L				
arithmetic mean (standard deviation)	-0.65 (± 25.997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Bilirubin

End point title	Total 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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	5
Units: µmol/L				
arithmetic mean (standard deviation)	-25.41 (± 5.596)	4.32 (± 26.094)	47.43 (± 51.076)	4.02 (± 10.439)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	2	85
Units: µmol/L				
arithmetic mean (standard deviation)	-25.08 (± 17.240)	-25.84 (± 19.893)	10.68 (± 20.258)	13.26 (± 37.239)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	109			
Units: µmol/L				
arithmetic mean (standard deviation)	9.57 (± 36.690)			

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	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	5
Units: U/L				
arithmetic mean (standard deviation)	13.09 (± 28.850)	-10.28 (± 6.589)	0.03 (± 32.694)	2.76 (± 7.848)

End point values	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	2	85
Units: U/L				
arithmetic mean (standard deviation)	-15.20 (± 23.355)	-2.52 (± 18.669)	-11.91 (± 35.318)	20.58 (± 46.589)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	109			
Units: U/L				
arithmetic mean (standard deviation)	15.50 (± 43.255)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet Response (ITT, HI-P Evaluable)

End point title	Platelet Response (ITT, HI-P Evaluable)[8]

End point description:

For subjects with baseline value of ≥ 20 × 10^9/L platelets, response was defined as a mean platelet increase of ≥ 30 × 10^9/L.
For subjects with baseline value of < 20 × 10^9/L, response was defined as a mean platelet increase of > 20 × 10^9/L with an increase of at least 100%.

End point type	Secondary

End point timeframe:

Any rolling 8-week interval.
Rolling 8 weeks is defined as any consecutive 8 weeks during the study.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The response rate for each dose group is reported in an 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	0.5 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)	Expansion Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	1	17
Units: Percent				
arithmetic mean (confidence interval 0.95%)	0 (0.0 to 97.5)	0 (0.0 to 84.2)	0 (0.0 to 97.5)	23.5 (6.8 to 49.9)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Percent				
arithmetic mean (confidence interval 0.95%)	19.0 (5.4 to 41.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pre-transfusion Hemoglobin Levels (ITT, HTB)

End point title	Pre-transfusion Hemoglobin Levels (ITT, HTB)

End point description:

Postbaseline Change from Baseline (g/dL)
The post-baseline pre-transfusion Hgb level was the average of all Hgb values recorded before each transfusion after the first dose of study drug.
The post-baseline change from Baseline was calculated as the postbaseline - baseline pre-transfusion Hgb level.

End point type	Other pre-specified

End point timeframe:

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

End point values	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)	0.75 milligrams per kilogram body weight (mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	3	2
Units: g/dL				
arithmetic mean (standard deviation)	-0.65 (± 0.57)	-0.46 (± 0.84)	0.06 (± 0.49)	0.41 (± 0.11)

End point values	1.00 milligrams per kilogram	1.33 milligrams per kilogram	1.75 milligrams per kilogram	Expansion Cohort

	body weight (mg/kg)	body weight (mg/kg)	body weight (mg/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	1	24
Units: g/dL				
arithmetic mean (standard deviation)	0.35 (± 0.83)	0.48 (± 0.36)	0.00 (± 0)	0.13 (± 0.94)

End point values	High-Transfusion Burden	Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	42		
Units: g/dL				
arithmetic mean (standard deviation)	0.13 (± 0.81)	0.13 (± 0.81)		

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 (N=116) are shown.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	0.125 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.125 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.25 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.25 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.5 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.5 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.00 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.00 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.33 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.33 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.75 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 1.75 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	Expansion Cohort
Reporting group description:	
Luspatercept starting dose 1.0 mg/kg subcutaneously (SC) once every 3 weeks. For each subsequent cycle in the expansion cohort (up to 5 cycles), a patient's dose level could be modified based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.75 mg/kg).	
Reporting group title	Total
Reporting group description:	
All subjects who received at least 1 dose of luspatercept.	

Serious adverse events	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transformation to acute myeloid leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Aortic valve stenosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis	Additional description: OLECRANI LEFT ARM (WORSENING)		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis	Additional description: BLEEDING IN BURSA OLECRANI, LEFT		

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transformation to acute myeloid leukaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Aortic valve stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis	Additional description: OLECRANI LEFT ARM (WORSENING)		
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis	Additional description: BLEEDING IN BURSA OLECRANI, LEFT		

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	14 / 89 (15.73%)	20 / 116 (17.24%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transformation to acute myeloid leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Aortic valve stenosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis	Additional description: OLECRANI LEFT ARM (WORSENING)		
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis	Additional description: BLEEDING IN BURSA OLECRANI, LEFT		

subjects affected / exposed	1 / 3 (33.33%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 89 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 89 (1.12%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	0.125 milligrams per kilogram body weight (mg/kg)	0.25 milligrams per kilogram body weight (mg/kg)	0.5 milligrams per kilogram body weight (mg/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	3 / 3 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	0.75 milligrams per kilogram body weight (mg/kg)	1.00 milligrams per kilogram body weight (mg/kg)	1.33 milligrams per kilogram body weight (mg/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	2 / 3 (66.67%)	3 / 6 (50.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0

Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	1.75 milligrams per kilogram body weight (mg/kg)	Expansion Cohort	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	75 / 89 (84.27%)	75 / 116 (64.66%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	19 / 89 (21.35%)	20 / 116 (17.24%)
occurrences (all)	0	19	20
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	9 / 89 (10.11%)	10 / 116 (8.62%)
occurrences (all)	0	9	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	11 / 89 (12.36%)	14 / 116 (12.07%)
occurrences (all)	0	11	14
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	6 / 89 (6.74%)	7 / 116 (6.03%)
occurrences (all)	0	6	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	5 / 89 (5.62%)	9 / 116 (7.76%)
occurrences (all)	0	5	9
Abdominal pain upper			

subjects affected / exposed	0 / 3 (0.00%)	4 / 89 (4.49%)	6 / 116 (5.17%)
occurrences (all)	0	4	6
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	6 / 89 (6.74%)	9 / 116 (7.76%)
occurrences (all)	0	6	9
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	5 / 89 (5.62%)	8 / 116 (6.90%)
occurrences (all)	0	5	8
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	5 / 89 (5.62%)	6 / 116 (5.17%)
occurrences (all)	1	5	6
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	11 / 89 (12.36%)	13 / 116 (11.21%)
occurrences (all)	0	11	13
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	6 / 89 (6.74%)	7 / 116 (6.03%)
occurrences (all)	0	6	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	Amendment #1: Dose escalation scheme modified to a 3+3 study design. Starting dose level revised to 0.125 mg/kg and subsequent cohort(s) maximum dose level will not exceed 1.0 mg/kg. Duration of patient participation updated to 28 weeks, with an increase in the follow-up period from 8 to 12 weeks. Inclusion criteria modified to clarify inclusion of patients who have no alternative treatment options. Inclusion criteria modified to clarify patient understands and is able to provide written informed consent. Replace Exclusion Criteria specifying exclusionary disorders with an Exclusion Criteria giving judgement to investigator.
29 August 2013	Changed definition of erythroid response in transfusion dependent patients to include a reduction of ≥ 4 units/8 weeks, which is consistent with the IWG guidelines for HI-E. Addition of FACT-An assessment as exploratory objective, exploratory endpoint. Increased number of cohorts from 5 to 7 and patient total from 60 to 72 to accomodate higher dose levels. Increased max dose from 1.0 mg/kg to 1.75 mg/kg. Inclusion criteria 3 modified to change definition of TD patients to include patients who recieve transfusions within 8 weeks prior to C1D1 for any reason. Addition of exclusion criteria to prevent enrollment of subjects previously treated with ACE-536 or sotatercept or transfusions within 7 days of C1D1. New post treatment follow up visit added. Dose-limiting toxicity was changed to treatment-emergent SAE of grade 3 or higher. ITT Population redefined to be consistent with safety population. EE population redefined to include maximum number of patients with evaluable data. Prolonged collection of transfusion history added. Toxicology section updated with information from ACE-536 IB Ver 004.
23 May 2014	Updated dose modification and titration rules for expansion cohort. Clarification added to birth control inclusion criteria. Additional pregnancy tests added to SOE. Clarification added that post treatment follow up visit to be performed +/- 7 days. Added 2 day window for Day 85 visit. Updated language to respresent currently ongoing toxicity studies in rabbits. Updated language implemented to provide objective measures for determining RBC transfusion requirements during ACE-536 treatment period. Dose modification rules updated to restrict dose reductions to dose levels tested in the escalation cohorts. Updated dose modification rules to replace 25% dose reductions with defined dose levels that were reviewed by the SRT in the escalation phase. Clarified that molecular testing of bone marrow aspirate may be performed. Updated to clarify that any available data prior to enrollment may be used to confirm eligibility. C1D1 results are not required to confirm eligibility.

22 July 2015	Addition of recently approved INN for investigational product. Addition of ability to include other QOL tools to evaluate patient outcomes. Approximately 50 additional patients split into two groups (2A and 2B) are to be enrolled, in order to gain experience in additional patient populations that have not been well represented by patients enrolled under the current protocol. Updated dose escalation table to reflect the addition of expansion cohort 2 and the planned total number of patients from 'up to 72' to 'up to 128'. Inclusion criteria updated to add enrollment criteria for expansion cohort 2 patients. Updated Study Drug Packaging, Labeling and Storage to include information on the lyophilized powder formulation which may be used in this study. Statistical language added to justify sample size of 50 patients in expansion cohort 2. Removed QoL Questionnaire at C5D1 for expansion cohort 2 patients only. Added transfusion frequency evaluation for the Post-Treatment Follow up visit. Clarification of the bone marrow aspirate/biopsy requirements for dose escalation in expansion cohort 1 and 2. Clarification that bone biomarkers are not required for expansion cohort 2 patients. Clarification of visit schedule for patients with dose delay. Updated to allow patients that have initiated iron chelation after C1D1 to continue on study. Provide further clarification on the use of "pre-transfusion hemoglobin threshold" during study. Updated Patient Dose with the starting dose of 1.0 mg/kg and the maximum dose level of 1.75 mg/kg. Revised dose administration limit to four injections and increased the volume per injection to accommodate doses with a total volume > 4 mL.
05 July 2016	Number of study centres increased from 15 to 20. Cohort definitions expanded to increase feasibility of enrollment of patients in expansion cohorts. Additional reason added for lack of effect for patients who have not clearly progressed, however are not receiving benefit from treatment. Removed restriction of requiring 24 hours between a RBC transfusion and dosing because no longer considered a risk. Language added to include option to delay patient dose. Language added to better define reporting of adverse events of special interest based on investigator's brochure.
05 July 2017	Medical monitor updated. Expansion cohort 3 added to enroll RS-, EPO < 500 U/L, transfused ≤ 6 RBC units, and ESA-naïve patients to further understand response to ACE-536 in this population. Total number of patients increased from 'up to 128' to 'up to 153' throughout to reflect addition of expansion cohort 3. Clarification added to Inclusion Criteria(s) to incorporate cohort specific requirements. Peripheral blasts added to hematology. Additional criteria added to comply with new additions to dose modification rules. WBC dose modification rule edited to detail actions to be taken to ensure patients are not treated if showing signs of disease progression. Additional dose modification rule added to ensure patients are not treated if showing signs of disease progression. Language and corresponding reference added to better clarify use of IPSS-R for assessment of adverse events of special interest. Providing details of IPSS-R scoring system due to addition of assessment of adverse events of special interest by IPSS-R.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported