



## Clinical trial results:

### A Phase 2, Open-Label, Ascending Dose Study to Evaluate the Effects of ACE-536 in Patients with -Thalassemia Intermedia

#### Summary

EudraCT number	2012-002499-15
Trial protocol	IT GR
Global end of trial date	11 November 2015

#### Results information

Result version number	v1 (current)
This version publication date	27 November 2016
First version publication date	27 November 2016

#### Trial information

##### Trial identification

Sponsor protocol code	A536-04
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01749540
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	Kenneth Attie, Acceleron Pharma Inc., 01 617 649 9200, kattie@acceleronpharma.com
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	17 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2015
Global end of trial reached?	Yes
Global end of trial date	11 November 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To evaluate the proportion of  $\beta$ -thalassemia patients who have an erythroid response, defined as: 1) a hemoglobin increase of  $\geq 1.5$  g/dL from baseline for  $\geq 14$  days (in the absence of red blood cell [RBC] transfusions) in non-transfusion dependent patients, or 2)  $\geq 20\%$  reduction in RBC transfusion burden compared to pretreatment in transfusion dependent patients.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Italy: 56
Worldwide total number of subjects	64
EEA total number of subjects	64

Notes:

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**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)	64
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

35 patients were enrolled in the dose-escalation phase in 6 cohorts of up to 6 patients each at dose levels (dl) of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.25 mg/kg for up to 5 cycles. 29 patients were enrolled in the expansion cohort and treated with a starting dose level of 0.8 mg/kg, dl was titrated based on the change in Hgb or patient transfusion burden.

### Pre-assignment

Screening details:

Patients who 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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	0.2 milligrams per kilogram body weight (mg/kg)

Arm description:

Luspatercept 0.2 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:

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

<b>Arm title</b>	0.4 mg/kg
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Arm description:

Luspatercept 0.4 mg/kg subcutaneously (SC) once every 3 weeks

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

Dosage and administration details:

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

<b>Arm title</b>	0.6 mg/kg
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Arm description:

Luspatercept 0.6 mg/kg subcutaneously (SC) once every 3 weeks

Arm type	Experimental
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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:	
Patients have received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.	
<b>Arm title</b>	0.8 mg/kg
Arm description:	
Luspatercept 0.8 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:	
Patients have received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.	
<b>Arm title</b>	1.0 mg/kg
Arm description:	
Luspatercept 1.0 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:	
Patients have received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.	
<b>Arm title</b>	1.25 mg/kg
Arm description:	
Luspatercept 1.25 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:	
Patients have received ACE-536, administered subcutaneously (SC), every 3 weeks for up to 5 cycles.	
<b>Arm title</b>	Expansion (0.8 mg/kg)
Arm description:	
Luspatercept starting dose 0.8 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 titrated based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.25 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

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**Dosage and administration details:**

The starting dose level for patients enrolled in the expansion cohort was 0.8 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 titrated based on the change in Hgb or transfusion burden for that patient. The maximum dose level given to a subject was 1.25 mg/kg.

Number of subjects in period 1	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg
Started	6	6	6
Completed	6	6	5
Not completed	0	0	1
Adverse event, non-fatal	-	-	1
Use of prohibited medications	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	0.8 mg/kg	1.0 mg/kg	1.25 mg/kg
Started	6	6	5
Completed	4	6	3
Not completed	2	0	2
Adverse event, non-fatal	2	-	-
Use of prohibited medications	-	-	1
Protocol deviation	-	-	1

Number of subjects in period 1	Expansion (0.8 mg/kg)
Started	29
Completed	26
Not completed	3
Adverse event, non-fatal	2
Use of prohibited medications	-
Protocol deviation	1

## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	64	64	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	64	64	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	38.1		
full range (min-max)	20 to 62	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	33	33	

## End points

### End points reporting groups

Reporting group title	0.2 milligrams per kilogram body weight (mg/kg)
Reporting group description:	
Luspatercept 0.2 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.4 mg/kg
Reporting group description:	
Luspatercept 0.4 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.6 mg/kg
Reporting group description:	
Luspatercept 0.6 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	0.8 mg/kg
Reporting group description:	
Luspatercept 0.8 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.0 mg/kg
Reporting group description:	
Luspatercept 1.0 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	1.25 mg/kg
Reporting group description:	
Luspatercept 1.25 mg/kg subcutaneously (SC) once every 3 weeks	
Reporting group title	Expansion (0.8 mg/kg)
Reporting group description:	
Luspatercept starting dose 0.8 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 titrated based on the change in Hgb or transfusion burden for that patient (the maximum dose level given was 1.25 mg/kg).	
Subject analysis set title	Non-Transfusion Dependent
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All treated patients who are Non-Transfusion Dependent at baseline.	
Non-Transfusion Dependence is defined as having received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1.	
In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	
Subject analysis set title	Transfusion Dependent
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All treated patients who are Transfusion Dependent at baseline.	
Transfusion Dependence is defined as requiring $\geq 4$ units of RBCs every 8 weeks (confirmed over 6 months prior to Cycle 1 Day 1).	
In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	
Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All treated patients	
In this study, Efficacy Evaluable population is the same as Intention-to-treat population.	

## Primary: Hemoglobin Response

End point title	Hemoglobin Response <sup>[1]</sup>
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End point description:

Consecutive change from baseline Hemoglobin  $\geq 1.5$  for  $\geq 14$  days in Non-Transfusion Dependent subjects.

End point type	Primary
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End point timeframe:

From first dose to last dose + 56 days.

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.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	3
Units: percent				
number (confidence interval 95%)	0 (0 to 45.9)	0 (0 to 45.9)	0 (0 to 52.2)	66.7 (9.4 to 99.2)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Non-Transfusion Dependent
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	1	10	33
Units: percent				
number (confidence interval 95%)	50 (1.3 to 98.7)	0 (0 to 97.5)	60 (26.2 to 87.8)	27.3 (13.3 to 45.5)

## Statistical analyses

No statistical analyses for this end point

## Primary: Transfusion Response

End point title	Transfusion Response <sup>[2]</sup>
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End point description:

$\geq 20\%$  reduction in RBC transfusion burden over 12 weeks, compared to pre-treatment, in transfusion dependent subjects

End point type	Primary
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End point timeframe:

First dose to last dose + 56 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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



Consequently, no p-value is reported in this section.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>	1	3
Units: percent				
number (confidence interval 95%)	( to )	( to )	100 (2.5 to 100)	66.7 (9.4 to 99.2)

Notes:

[3] - No subjects

[4] - No subjects

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Transfusion Dependent
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	4	19	31
Units: percent				
number (confidence interval 95%)	100 (39.8 to 100)	75 (19.4 to 99.4)	78.9 (54.4 to 93.9)	80.6 (62.5 to 92.5)

## Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

First dose to End of Treatment visit

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	6	6
Units: percent				
arithmetic mean (standard deviation)	-35.09 (± 10.94)	15.45 (± 56.2)	17.7 (± 9.31)	20.08 (± 20.77)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	3	20	51
Units: percent				
arithmetic mean (standard deviation)	0.65 (± 10.18)	-0.17 (± 17.15)	19.01 (± 41.1)	10.04 (± 35.39)

### Statistical analyses

No statistical analyses for this end point

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

End point title	CTX - End of Treatment - Percent Change from Baseline
End point description:	
End point type	Secondary
End point timeframe:	
First dose to End of treatment visit.	

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	6
Units: percent				
arithmetic mean (standard deviation)	42.56 (± 14.52)	3.39 (± 53.02)	8.43 (± 31.32)	23.61 (± 33.31)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	3	20	44
Units: percent				
arithmetic mean (standard deviation)	12.67 (± 53.27)	-20.87 (± 31.86)	22.62 (± 59.97)	16.74 (± 49.73)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Erythropoietin - End of Treatment - Change from Baseline

End point title	Erythropoietin - End of Treatment - Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: IU/L				
arithmetic mean (standard deviation)	-18.67 (± 42.95)	6.85 (± 41.82)	21.88 (± 66.23)	37.1 (± 48.79)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	56
Units: IU/L				
arithmetic mean (standard deviation)	71.62 (± 104.86)	64.58 (± 94.47)	40.92 (± 109.54)	33.41 (± 87.47)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Reticulocytes - End of Treatment - Change from Baseline

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

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	6	5
Units: 10 <sup>9</sup> /L				
arithmetic mean (standard deviation)	-10.8 (±	0.63 (± 1.63)	-34.42 (±	15.77 (±

28.69)

73.88)

17.45)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	28	58
Units: 10 <sup>9</sup> /L				
arithmetic mean (standard deviation)	16.9 (± 46.62)	297.57 (± 330.75)	39.87 (± 219.87)	38.82 (± 187.14)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Iron - End of Treatment - Percent Change from Baseline

End point title	Serum Iron - End of Treatment - Percent Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	-15.78 (± 26.9)	-8.99 (± 38.02)	7.81 (± 15.09)	-12.93 (± 31.55)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	24	58
Units: percent				
arithmetic mean (standard deviation)	-5.37 (± 35.75)	-12.38 (± 18.35)	2.67 (± 41.64)	-3.4 (± 34.51)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Iron Binding Capacity(TIBC) - End of Treatment - Percent Change from Baseline

End point title	Total Iron Binding Capacity(TIBC) - End of Treatment - Percent Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	2.91 (± 7.02)	-1.53 (± 7.37)	3.53 (± 7.85)	-4.86 (± 11.67)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	24	58
Units: percent				
arithmetic mean (standard deviation)	-2.13 (± 6.18)	-0.76 (± 4.3)	1.25 (± 12.7)	0.25 (± 10.09)

### Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	3.96 (± 6.73)	-1.54 (± 6.04)	3.04 (± 8.51)	-4.71 (± 11.26)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	24	58
Units: percent				
arithmetic mean (standard deviation)	-0.99 (± 7.51)	-1.64 (± 5.59)	0.98 (± 12.01)	0.27 (± 9.76)

### Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	3.61 (± 10.91)	-10.6 (± 12.29)	10.55 (± 34.45)	36.29 (± 41.28)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	24	58

Units: percent				
arithmetic mean (standard deviation)	68.17 (± 60.44)	83.34 (± 90.42)	53.25 (± 57.3)	38.96 (± 56.06)

### Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	-18.48 (± 17.77)	8.43 (± 27.22)	-4.5 (± 14.92)	-23.73 (± 27.83)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	24	58
Units: percent				
arithmetic mean (standard deviation)	-23.17 (± 19.41)	-25.18 (± 22.75)	-27.46 (± 18.67)	-19.46 (± 22.79)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hepcidin - End of Treatment - Percent Change from Baseline

End point title	Hepcidin - End of Treatment - Percent Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	5	5
Units: percent				
arithmetic mean (standard deviation)	7.48 (± 41.12)	58.35 (± 140.97)	-4.81 (± 27.81)	0.67 (± 83.3)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	1	5	31
Units: percent				
arithmetic mean (standard deviation)	-41.16 (± 12.73)	-13.58 (± 0)	-12.54 (± 23.44)	4.06 (± 74.77)

### Statistical analyses

No statistical analyses for this end point

### Secondary: LIC - End of Treatment - Change from Baseline

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

End point description:

End point type Secondary

End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	5
Units: mg/g dw				
arithmetic mean (standard deviation)	-0.01 (± 0.61)	-0.46 (± 1.17)	-1.25 (± 1.54)	-0.88 (± 0.97)



End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	3	25	55
Units: mg/g dw				
arithmetic mean (standard deviation)	-1.7 (± 3.57)	-0.1 (± 0.7)	0.16 (± 1.02)	-0.35 (± 1.58)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hb A - End of Treatment - Change from Baseline

End point title	Hb A - End of Treatment - Change from Baseline
End point description:	
End point type	Secondary
End point timeframe:	
First dose to End of treatment visit.	

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	5	5
Units: g/dL				
arithmetic mean (standard deviation)	-0.07 (± 0.61)	0.27 (± 0.57)	0.04 (± 2.11)	-0.35 (± 1.98)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	64
Units: g/dL				
arithmetic mean (standard deviation)	-1.11 (± 1.45)	-0.76 (± 0.5)	-0.57 (± 1.11)	-0.44 (± 1.26)

### Statistical analyses

No statistical analyses for this end point

**Secondary: Hb A2 - End of Treatment - Change from Baseline**

End point title	Hb A2 - End of Treatment - Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	5
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0.1)	-0.18 (± 0.5)	0.1 (± 0.13)	-0.06 (± 0.31)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	53
Units: g/dL				
arithmetic mean (standard deviation)	0.06 (± 0.05)	0.04 (± 0.03)	0.03 (± 0.06)	0.01 (± 0.19)

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Hb C - End of Treatment - Change from Baseline**

End point title	Hb C - End of Treatment - Change from Baseline
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End point description:

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	5
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	53
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hb D - End of Treatment - Change from Baseline

End point title	Hb D - End of Treatment - Change from Baseline
End point description:	
End point type	Secondary
End point timeframe:	
First dose to End of treatment visit.	

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	5
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	53
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hb F - End of Treatment - Change from Baseline

End point title Hb F - End of Treatment - Change from Baseline

End point description:

End point type Secondary

End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: g/dL				
arithmetic mean (standard deviation)	0.09 (± 0.1)	-0.23 (± 0.43)	0.87 (± 1.57)	0.24 (± 0.53)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	5	3	22	50
Units: g/dL				
arithmetic mean (standard deviation)	1.54 (± 1.31)	0.84 (± 0.16)	0.6 (± 0.78)	0.55 (± 0.9)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hb S - End of Treatment - Change from Baseline

End point title Hb S - End of Treatment - Change from Baseline

End point description:

End point type Secondary

End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	5
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	22	53
Units: g/dL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

### Statistical analyses

No statistical analyses for this end point

### Secondary: HBA12 - End of Treatment - Change from Baseline

End point title HBA12 - End of Treatment - Change from Baseline

End point description:

End point type Secondary

End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	2	5
Units: g/dL				
arithmetic mean (standard deviation)	0.69 (± 0.64)	-2.58 (± 2.01)	0.67 (± 0.51)	0.41 (± 0.78)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	12	40
Units: g/dL				
arithmetic mean (standard deviation)	3.55 (± 2.4)	-1.96 (± 3.78)	2.13 (± 1.57)	0.84 (± 2.65)

### Statistical analyses

No statistical analyses for this end point

### Secondary: HBB - End of Treatment - Change from Baseline

End point title	HBB - End of Treatment - Change from Baseline
End point description:	
End point type	Secondary
End point timeframe:	
First dose to End of treatment visit.	

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	2	5
Units: g/dL				
arithmetic mean (standard deviation)	0.12 (± 0.12)	-0.15 (± 0.16)	0.06 (± 0.08)	0.06 (± 0.25)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	12	40
Units: g/dL				
arithmetic mean (standard deviation)	0.33 (± 0.51)	-0.41 (± 0.72)	0.46 (± 0.34)	0.16 (± 0.45)

### Statistical analyses

No statistical analyses for this end point

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

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

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

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	6	6
Units: /100 WBC				
arithmetic mean (standard deviation)	38.75 (± 57.64)	-4 (± 70.52)	16.67 (± 26.03)	20.67 (± 55.72)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	5	4	23	54
Units: /100 WBC				
arithmetic mean (standard deviation)	37 (± 46.92)	44.5 (± 44.17)	57.48 (± 93.65)	37.78 (± 73.38)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Haptoglobin - End of Treatment - Change from Baseline

End point title	Haptoglobin - End of Treatment - Change from Baseline
End point description:	

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

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	4	5	3
Units: mg/dL				
arithmetic mean (standard deviation)	1.2 (± 5.63)	3.8 (± 4.06)	-0.56 (± 0.93)	-3 (± 3)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	4	13	38
Units: mg/dL				
arithmetic mean (standard deviation)	-9 (± 8.29)	-15.75 (± 12.37)	-8.15 (± 14.11)	-5.15 (± 11.05)

## Statistical analyses

No statistical analyses for this end point

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

End point title	LDH - End of Treatment - Percent Change from Baseline
End point description:	
End point type	Secondary
End point timeframe:	
First dose to End of treatment visit.	

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	0.43 (± 17.52)	-0.95 (± 10.49)	8.68 (± 25.13)	29.17 (± 25.18)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	28	62
Units: percent				
arithmetic mean (standard deviation)	37.38 (± 64.52)	53.79 (± 68.18)	44.95 (± 68.53)	31 (± 56.18)

## Statistical analyses



No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

First dose to End of treatment visit.

End point values	0.2 milligrams per kilogram body weight (mg/kg)	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percent				
arithmetic mean (standard deviation)	13.88 (± 23.72)	-25.18 (± 18.27)	4.77 (± 8.68)	6.29 (± 20.29)

End point values	1.0 mg/kg	1.25 mg/kg	Expansion (0.8 mg/kg)	Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	29	63
Units: percent				
arithmetic mean (standard deviation)	3.68 (± 21.42)	2.76 (± 53.64)	18.33 (± 38.67)	8.94 (± 33.57)

### 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  $\geq 5\%$  of subjects overall (N=64) are shown.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	0.2 mg/kg
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Reporting group description: -

Reporting group title	0.4 mg/kg
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Reporting group description: -

Reporting group title	0.6 mg/kg
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Reporting group description: -

Reporting group title	0.8 mg/kg
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Reporting group description: -

Reporting group title	1.0 mg/kg
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Reporting group description: -

Reporting group title	1.25 mg/kg
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Reporting group description: -

Reporting group title	Expansion
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Reporting group description: -

Serious adverse events	0.2 mg/kg	0.4 mg/kg	0.6 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Bone marrow failure	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	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

Serious adverse events	0.8 mg/kg	1.0 mg/kg	1.25 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Bone marrow failure	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (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

<b>Serious adverse events</b>	Expansion		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Bone marrow failure	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	0.2 mg/kg	0.4 mg/kg	0.6 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	6 / 6 (100.00%)	5 / 6 (83.33%)
Injury, poisoning and procedural complications			
Post-traumatic pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Nervous system disorders			
Headache	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	0	1	3
General disorders and administration site conditions			
Asthenia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Oedema peripheral	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
	occurrences (all)	1	0
Pyrexia	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)
	occurrences (all)	1	2
Gastrointestinal disorders			
Diarrhoea	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
	occurrences (all)	1	0
Nausea	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	1
Oropharyngeal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)
	occurrences (all)	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)
	occurrences (all)	0	2
Back pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	0
Bone pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	0
Musculoskeletal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
	occurrences (all)	0	1

Myalgia	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)
	occurrences (all)	1	2
Infections and infestations			
Influenza	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
	occurrences (all)	0	0
Nasopharyngitis	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	1
Pharyngitis	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)
	occurrences (all)	1	0
Rhinitis	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)
	occurrences (all)	0	1

<b>Non-serious adverse events</b>	0.8 mg/kg	1.0 mg/kg	1.25 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	5 / 5 (100.00%)
Injury, poisoning and procedural complications			
Post-traumatic pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)
	occurrences (all)	0	1
Nervous system disorders			
Headache	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)
	occurrences (all)	3	4
General disorders and administration site conditions			
Asthenia	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)
	occurrences (all)	3	2
Oedema peripheral	Additional description: 'Occurrences all number' equal to subjects affected number.		
	subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)
	occurrences (all)	2	2

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Pyrexia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Nausea	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	2 / 5 (40.00%) 2
Oropharyngeal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	1 / 5 (20.00%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	2 / 5 (40.00%) 2
Back pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Bone pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 4	2 / 6 (33.33%) 2	3 / 5 (60.00%) 3
Musculoskeletal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1
Myalgia	Additional description: 'Occurrences all number' equal to subjects affected number.		

subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	0 / 6 (0.00%) 0	2 / 5 (40.00%) 2
Infections and infestations			
Influenza	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 6 (33.33%) 2	2 / 5 (40.00%) 2
Nasopharyngitis	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Pharyngitis	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Rhinitis			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	2 / 5 (40.00%) 2

<b>Non-serious adverse events</b>	Expansion		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 29 (89.66%)		
Injury, poisoning and procedural complications			
Post-traumatic pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Nervous system disorders			
Headache	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	8 / 29 (27.59%) 8		
General disorders and administration site conditions			
Asthenia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	11 / 29 (37.93%) 11		
Oedema peripheral	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Pyrexia	Additional description: 'Occurrences all number' equal to subjects affected number.		

	number.		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Nausea	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Oropharyngeal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	7		
Back pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	6		
Bone pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	14 / 29 (48.28%)		
occurrences (all)	14		
Musculoskeletal pain	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	7		
Myalgia	Additional description: 'Occurrences all number' equal to subjects affected number.		
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	6		



Infections and infestations			
Influenza		Additional description: 'Occurrences all number' equal to subjects affected number.	
subjects affected / exposed		1 / 29 (3.45%)	
occurrences (all)		1	
Nasopharyngitis		Additional description: 'Occurrences all number' equal to subjects affected number.	
subjects affected / exposed		2 / 29 (6.90%)	
occurrences (all)		2	
Pharyngitis		Additional description: 'Occurrences all number' equal to subjects affected number.	
subjects affected / exposed		0 / 29 (0.00%)	
occurrences (all)		0	
Rhinitis			
subjects affected / exposed		2 / 29 (6.90%)	
occurrences (all)		2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2012	AMENDMENT 01: revise inclusion criteria to be consistent with the accepted standard definition of the $\beta$ -thalassemia intermedia patient population; addition of Urinalysis to the end of study visit.
09 April 2013	AMENDMENT 02: addition of patients with transfusion dependent $\beta$ -thalassemia intermedia, including eligibility, revising endpoints and collection of transfusion data; eligibility to exclude prior treatment with ACE-011 (sotatercept) or ACE-536 (luspatercept).
27 November 2013	AMENDMENT 03: allow enrollment of patients with $\beta$ -thalassemia major in the expansion cohort; add two further dose levels, increase total number of planned patients.
07 November 2014	AMENDMENT 04: add exploratory objectives, provide clarification on required birth control methods (revised inclusion criterion #7); increase the washout from hydroxyurea (revised exclusion criterion #15), include additional evaluations and safety criteria; include expanded dose modification rules.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported