



## 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 |
|-----------------------|---------|

##### 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 |
| Scientific contact           | Kenneth Attie, Acceleron Pharma Inc., 01 617 649 9200, kattie@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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| 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**

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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**

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**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 |
|------------------|-----------|

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 |
|------------------|-----------|

Arm description:

Luspatercept 0.6 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>   | 0.8 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<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>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> |
|-----------------|------------------------------------|

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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> |
|-----------------|-------------------------------------|

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 |
|----------------|---------|

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 |
|-----------------|--|

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   | 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 |
|-----------------|--|

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: 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 |
|-----------------|---|

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          | 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 |
|-----------------|--|

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) | -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 |
|-----------------|---|

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) | 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 |
|-----------------|---|

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) | 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 |
|-----------------|--|

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) | 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 ( $\pm$ 60.44) | 83.34 ( $\pm$ 90.42) | 53.25 ( $\pm$ 57.3) | 38.96 ( $\pm$ 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 |
|-----------------|--|

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) | -18.48 ( $\pm$ 17.77)                           | 8.43 ( $\pm$ 27.22) | -4.5 ( $\pm$ 14.92) | -23.73 ( $\pm$ 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 ( $\pm$ 19.41) | -25.18 ( $\pm$ 22.75) | -27.46 ( $\pm$ 18.67) | -19.46 ( $\pm$ 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 |
|-----------------|--|

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   | 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 |
|-----------------|---|

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 (± 0.1)                                       | -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 |
|-----------------|--|

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 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 ( $\pm$ 8.29) | -15.75 ( $\pm$ 12.37) | -8.15 ( $\pm$ 14.11)  | -5.15 ( $\pm$ 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 ( $\pm$ 17.52)                             | -0.95 ( $\pm$ 10.49) | 8.68 ( $\pm$ 25.13) | 29.17 ( $\pm$ 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 ( $\pm$ 64.52) | 53.79 ( $\pm$ 68.18) | 44.95 ( $\pm$ 68.53)  | 31 ( $\pm$ 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 |
|-----------------|--|

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) | 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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | 0.2 mg/kg |
|-----------------------|-----------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | 0.4 mg/kg |
|-----------------------|-----------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | 0.6 mg/kg |
|-----------------------|-----------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | 0.8 mg/kg |
|-----------------------|-----------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | 1.0 mg/kg |
|-----------------------|-----------|

Reporting group description: -

|                       |            |
|-----------------------|------------|
| Reporting group title | 1.25 mg/kg |
|-----------------------|------------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | Expansion |
|-----------------------|-----------|

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

|  |   |                     |                     |
|--|---|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 6 (50.00%)<br>3   | 0 / 6 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2 |
| Infections and infestations                      |   |                     |                     |
| Influenza  | Additional description: 'Occurrences all number' equal to subjects affected number. |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 2 / 6 (33.33%)<br>2 | 2 / 5 (40.00%)<br>2 |
| Nasopharyngitis                                  | Additional description: 'Occurrences all number' equal to subjects affected number. |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Pharyngitis                                      | Additional description: 'Occurrences all number' equal to subjects affected number. |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1   | 1 / 6 (16.67%)<br>1 | 0 / 5 (0.00%)<br>0  |
| Rhinitis   |   |                     |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 2 / 5 (40.00%)<br>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<br>occurrences (all)      | 1 / 29 (3.45%)<br>1   |  |  |
| Nervous system disorders                              |   |  |  |
| Headache  | Additional description: 'Occurrences all number' equal to subjects affected number. |  |  |
| subjects affected / exposed<br>occurrences (all)      | 8 / 29 (27.59%)<br>8  |  |  |
| General disorders and administration site conditions  |   |  |  |
| Asthenia  | Additional description: 'Occurrences all number' equal to subjects affected number. |  |  |
| subjects affected / exposed<br>occurrences (all)      | 11 / 29 (37.93%)<br>11  |  |  |
| Oedema peripheral                                     | Additional description: 'Occurrences all number' equal to subjects affected number. |  |  |
| subjects affected / exposed<br>occurrences (all)      | 3 / 29 (10.34%)<br>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<br>Influenza<br>subjects affected / exposed<br>occurrences (all) | Additional description: 'Occurrences all number' equal to subjects affected number.<br>1 / 29 (3.45%)<br>1 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: 'Occurrences all number' equal to subjects affected number.<br>2 / 29 (6.90%)<br>2 |  |  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: 'Occurrences all number' equal to subjects affected number.<br>0 / 29 (0.00%)<br>0 |  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                 | 2 / 29 (6.90%)<br>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