



Clinical trial results:

A Phase 2, Exploratory, Placebo-Controlled, Multicenter, Double-Blind Evaluation of the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Effects of Five Dose Regimens of Aes-103 Given for 28 Days to Subjects with Stable Sickle Cell Disease

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001534-18 |
| Trial protocol | GB |
| Global end of trial date | 16 March 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 19 March 2016 |
| First version publication date | 19 March 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | Aes-103-003 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01987908 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Baxalta US Inc. |
| Sponsor organisation address | One Baxter Way, Westlake Village, United States, CA 91362-3811 |
| Public contact | Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com |
| Sponsor organisation name | Baxalta Innovations GmbH |
| Sponsor organisation address | Industriestrasse 67, Vienna, Austria, 1221 |
| Public contact | Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 December 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 March 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 March 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and PK profile of five dosing regimens of Aes-103 (1000 mg four times a day [q.i.d.] in Cohort A and up to four higher or lower dosing regimens in Cohort B) for up to 28 days in adult subjects with stable sickle cell disease compared with subjects receiving placebo.

Protection of trial subjects:

The study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application), and International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 03 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Worldwide total number of subjects | 23 |
| EEA total number of subjects | 23 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|----|
| Adults (18-64 years) | 23 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 6 clinical sites in the United Kingdom.

Pre-assignment

Screening details:

Of 35 enrolled subjects, 12 were screen failures. Of 23 subjects who started the 2-week, single-blind, outpatient, placebo lead-in period (where all subjects received placebo treatment to obtain stable baseline values and to screen out subjects who did not tolerate placebo or were not compliant with study procedures), 9 subjects were discontinued.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 23 |
| Number of subjects completed | 14 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Adverse event, non-fatal: 2 |
| Reason: Number of subjects | Physician decision: 2 |
| Reason: Number of subjects | Study termination by Sponsor: 4 |
| Reason: Number of subjects | Consent withdrawn by subject: 1 |

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Double-Blind Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Blinding implementation details:

To maintain blinding of the subjects and the clinical team, the unblinded pharmacist consulted the randomization sequence and dispensed the appropriate blinded bottles of solutions containing study drug or placebo.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Study Drug |

Arm description:

Subjects randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Aes-103 |
| Investigational medicinal product code | |
| Other name | 5-hydroxymethyl furfural (5-HMF) |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

liquid oral formulation

| | |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description:

Subjects randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|---|---------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |
| Dosage and administration details: liquid oral formulation | |

| Number of subjects in period 1^[1] | Study Drug | Placebo |
|---|------------|---------|
| Started | 11 | 3 |
| Completed | 10 | 2 |
| Not completed | 1 | 1 |
| Adverse event, non-fatal | 1 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of 35 enrolled subjects, 12 were screen failures. Of 23 subjects who started the 2-week, single-blind, outpatient, placebo lead-in period (where all subjects received placebo treatment to obtain stable baseline values and to screen out subjects who did not tolerate placebo or were not compliant with study procedures), 9 subjects were discontinued.

Period 2

| | |
|------------------------------|-----------------------------------|
| Period 2 title | Post-Treatment Observation Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Blinding implementation details:

Subjects received double-blind treatment during the 28-day treatment period.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Study Drug |

Arm description:

In the double-blind treatment period, subjects were randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Aes-103 |
| Investigational medicinal product code | |
| Other name | 5-hydroxymethyl furfural (5-HMF) |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

liquid oral formulation

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

In the double-blind treatment period, subjects were randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

liquid oral formulation

| Number of subjects in period 2 | Study Drug | Placebo |
|---------------------------------------|------------|---------|
| Started | 10 | 2 |
| Completed | 7 | 2 |
| Not completed | 3 | 0 |
| Bad veins | 1 | - |
| Study withheld by the sponsor | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Double-Blind Treatment Period |
|-----------------------|-------------------------------|

Reporting group description:

Treatment (Cohort A)

| Reporting group values | Double-Blind Treatment Period | Total | |
|--|-------------------------------|-------|--|
| Number of subjects | 14 | 14 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 85 years and over | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| Adults (18-64 years) | 14 | 14 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| In utero | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 28 | | |
| standard deviation | ± 6 | - | |
| Gender categorical | | | |
| Units: | | | |
| Female | 8 | 8 | |
| Male | 6 | 6 | |

Subject analysis sets

| | |
|----------------------------|-------------------------------|
| Subject analysis set title | Double-blind treatment (n=14) |
|----------------------------|-------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects treated in the double-blind treatment period (ie, randomized to study drug or placebo), Day 1 to Day 28

| | |
|----------------------------|------------------------------|
| Subject analysis set title | Treatment: Study Drug (n=11) |
|----------------------------|------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Double-blind treatment period: 1000 mg of study drug QID (every 6 hours)

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Treatment: Placebo (n=3) |
|----------------------------|--------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Double-blind treatment period: 1000 mg of placebo QID (every 6 hours)

| | |
|----------------------------|-------------------------------|
| Subject analysis set title | Placebo lead-in period (n=23) |
|----------------------------|-------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects who received at least 1 dose of placebo in the lead-in period, ie, prior to the double-blind treatment period, Day -14 to Day -1

| | |
|----------------------------|--|
| Subject analysis set title | Post-treatment observation period (n=12) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects who completed the double-blind treatment period and entered the post-treatment observation period, Day 29 to Day 49

| Reporting group values | Double-blind treatment (n=14) | Treatment: Study Drug (n=11) | Treatment: Placebo (n=3) |
|--|-------------------------------|------------------------------|--------------------------|
| Number of subjects | 14 | 11 | 3 |
| Age categorical Units: Subjects | | | |
| 85 years and over | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| Adults (18-64 years) | 14 | 11 | 3 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| In utero | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 28 | 29 | 25 |
| standard deviation | ± 6 | ± 6 | ± 3 |
| Gender categorical Units: | | | |
| Female | 8 | 8 | 0 |
| Male | 6 | 3 | 3 |

| Reporting group values | Placebo lead-in period (n=23) | Post-treatment observation period (n=12) | |
|--|-------------------------------|--|--|
| Number of subjects | 23 | 12 | |
| Age categorical Units: Subjects | | | |
| 85 years and over | 0 | | |
| From 65-84 years | 0 | | |
| Adults (18-64 years) | 23 | | |
| Adolescents (12-17 years) | 0 | | |
| Children (2-11 years) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| In utero | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | 28 | | |
| standard deviation | ± 7 | ± | |

| | | | |
|--------------------|----|--|--|
| Gender categorical | | | |
| Units: | | | |
| Female | 13 | | |
| Male | 10 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Study Drug |
| Reporting group description: | |
| Subjects randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days | |
| Reporting group title | Study Drug |
| Reporting group description: | |
| In the double-blind treatment period, subjects were randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days | |
| Reporting group title | Placebo |
| Reporting group description: | |
| In the double-blind treatment period, subjects were randomized 3:1 to receive 4 times daily dosing of 1,000 mg of Aes-103 or placebo for 28 days | |
| Subject analysis set title | Double-blind treatment (n=14) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Subjects treated in the double-blind treatment period (ie, randomized to study drug or placebo), Day 1 to Day 28 | |
| Subject analysis set title | Treatment: Study Drug (n=11) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Double-blind treatment period: 1000 mg of study drug QID (every 6 hours) | |
| Subject analysis set title | Treatment: Placebo (n=3) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Double-blind treatment period: 1000 mg of placebo QID (every 6 hours) | |
| Subject analysis set title | Placebo lead-in period (n=23) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Subjects who received at least 1 dose of placebo in the lead-in period, ie, prior to the double-blind treatment period, Day -14 to Day -1 | |
| Subject analysis set title | Post-treatment observation period (n=12) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Subjects who completed the double-blind treatment period and entered the post-treatment observation period, Day 29 to Day 49 | |

Primary: Frequency and severity of adverse events, including sickle-cell specific symptoms, during the double-blind treatment period (Day 1 to Day 28)

| | |
|--|--|
| End point title | Frequency and severity of adverse events, including sickle-cell specific symptoms, during the double-blind treatment period (Day 1 to Day 28) ^[1] |
| End point description: | |
| Measurement of spontaneously reported adverse events during the double-blind treatment period. Sickle-cell specific symptoms included the development of new skin ulcers, hospitalization or ambulatory acute care, intravenous analgesics visit for pain episodes (ie, sickle-cell disease related pain), acute chest syndrome, priapism, and stroke. | |
| End point type | Primary |
| End point timeframe: | |
| 28 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: Per protocol, descriptive statistics were collected for this endpoint.

| End point values | Study Drug | Placebo | Double-blind treatment (n=14) | |
|------------------------------------|-----------------|-----------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 11 | 3 | 14 | |
| Units: subjects | | | | |
| Treatment-emergent AEs | 9 | 3 | 12 | |
| Related AEs | 8 | 2 | 10 | |
| Serious AEs | 0 | 0 | 0 | |
| Severe AEs | 0 | 0 | 0 | |
| AEs leading to discontinuation | 1 | 1 | 2 | |
| AEs leading to death | 0 | 0 | 0 | |
| Sickle-cell specific complications | 4 | 1 | 5 | |

Statistical analyses

No statistical analyses for this end point

Primary: Frequency and severity of adverse events, including sickle-cell specific symptoms, during the placebo lead-in period (Day -14 to Day -1)

| | |
|-----------------|---|
| End point title | Frequency and severity of adverse events, including sickle-cell specific symptoms, during the placebo lead-in period (Day -14 to Day -1) ^[2] |
|-----------------|---|

End point description:

Measurement of spontaneously reported adverse events during the placebo lead-in period.

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

End point timeframe:

14 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: Per protocol, descriptive statistics were collected for this endpoint.

| End point values | Placebo lead-in period (n=23) | | | |
|------------------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 23 | | | |
| Units: subjects | | | | |
| Treatment-emergent AEs | 21 | | | |
| Related AEs | 12 | | | |
| Serious AEs | 2 | | | |
| Severe AEs | 2 | | | |
| AEs leading to discontinuation | 2 | | | |
| AEs leading to death | 0 | | | |
| Sickle-cell specific complications | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Frequency and severity of adverse events, including sickle-cell specific symptoms, during the post-treatment observation period (Day 29 to Day 49)

| | |
|-----------------|---|
| End point title | Frequency and severity of adverse events, including sickle-cell specific symptoms, during the post-treatment observation period (Day 29 to Day 49) ^[3] |
|-----------------|---|

End point description:

Measurement of spontaneously reported adverse events during the post-treatment observation period.

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

End point timeframe:

21 days

Notes:

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

Justification: Per protocol, descriptive statistics were collected for this endpoint.

| End point values | Study Drug | Placebo | Post-treatment observation period (n=12) | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 2 | 12 | |
| Units: subjects | | | | |
| Treatment-emergent AEs | 4 | 0 | 4 | |
| Related AEs | 2 | 0 | 2 | |
| Serious AEs | 1 | 0 | 1 | |
| Severe AEs | 1 | 0 | 1 | |
| AEs leading to discontinuation | 0 | 0 | 0 | |
| AEs leading to death | 0 | 0 | 0 | |
| Sickle-cell specific complications | 1 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Primary: Sickle-Cell Disease-Related Symptoms

| | |
|-----------------|---|
| End point title | Sickle-Cell Disease-Related Symptoms ^[4] |
|-----------------|---|

End point description:

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

End point timeframe:

Throughout study, total of approximately 9 weeks

Notes:

[4] - 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: Per protocol, descriptive statistics were collected for this endpoint.

| End point values | Treatment: Study Drug (n=11) | Treatment: Placebo (n=3) | | |
|---|------------------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: subjects | | | | |
| Abdominal Pain - Sickle Pain | 1 | 0 | | |
| Exacerbation of Sickle Cell (SC) Disease Pain | 1 | 0 | | |
| SC Disease Related Pain | 3 | 0 | | |
| SC Pain | 3 | 1 | | |
| SC-nonspecific: Back Pain | 1 | 0 | | |
| SC-nonspecific: Body Pain | 1 | 0 | | |
| SC-nonspecific: Headache | 5 | 1 | | |
| SC-nonspecific: Migraine | 1 | 0 | | |
| SC-nonspecific: T Wave inversion | 1 | 0 | | |
| SC-nonspecific: Transaminitis | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resting oxygen saturation as measured by oximetry (SpO2) - Change from baseline

| | |
|-----------------|---|
| End point title | Resting oxygen saturation as measured by oximetry (SpO2) - Change from baseline |
|-----------------|---|

End point description:

A measure of the amount of oxygen in the blood. Oxygen saturation was determined by pulse oximetry. A pulse oximeter was placed over a nail polish-free finger nail to determine peripheral oxygen saturation (SpO2). Baseline was defined as the most recent value obtained prior to the start of dosing on Day 1 of the double-blind dosing period. A mean change from baseline >0 indicates an increase in oxygen saturation, a mean change <0 indicates a decrease in oxygen saturation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline, Day 4, Day 7, Day 14, Day 28.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: Percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 4 | 0 (± 2) | 4 (± 5) | | |
| Day 7 | 0 (± 2) | -4 (± 8) | | |

| | | | | |
|--------|--------------|---------------|--|--|
| Day 14 | 0 (\pm 2) | 8 (\pm 10) | | |
| Day 28 | 0 (\pm 3) | 6 (\pm 8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Oxygen binding p50/p20 value - Change from baseline

| | |
|-----------------|---|
| End point title | Oxygen binding p50/p20 value - Change from baseline |
|-----------------|---|

End point description:

A measure of the ability of hemoglobin to bind oxygen. The p50 is the oxygen level at which 50% of the hemoglobin contains oxygen. The p20 is the oxygen level at which 20% of the hemoglobin contains oxygen. Baseline is defined as the most recent value obtained prior to start of dosing on Day 1 of the double-blind dosing period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

7 days

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: Percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 0 (\pm 0.2) | 0 (\pm 0.2) | | |
| Day 4 | 0 (\pm 0.1) | 0.1 (\pm 0.1) | | |
| Day 7 | 0 (\pm 0.2) | 0 (\pm 0.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma erythropoietin (EPO) levels - Change from baseline

| | |
|-----------------|---|
| End point title | Plasma erythropoietin (EPO) levels - Change from baseline |
|-----------------|---|

End point description:

Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow. EPO can be detected and measured in the blood.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured at baseline and at Day 28

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 2 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | -5.9 (± 50.3) | -15.1 (± 20.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hematocrit levels - Change from baseline

| | |
|---|--|
| End point title | Hematocrit levels - Change from baseline |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline, Day 1, Day 4, Day 7, Day 14, Day 28. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[5] | 3 ^[6] | | |
| Units: L/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 0.006 (± 0.011) | -0.002 (± 0.007) | | |
| Day 7 | 0.007 (± 0.013) | 0.02 (± 0.01) | | |
| Day 14 | 0.003 (± 0.013) | -0.006 (± 0.015) | | |
| Day 28 | 0.011 (± 0.012) | 0.006 (± 0.007) | | |

Notes:

[5] - Day 1: n=11, Day 7: n=9, Day 14: n=8, Day 28: n=8

[6] - Day 1: n=3, Day 7: n=3, Day 14: n=2, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Lactate dehydrogenase (LDH) levels - Change from baseline

| | |
|--|---|
| End point title | Lactate dehydrogenase (LDH) levels - Change from baseline |
| End point description: | |
| LDH levels were measured as a biomarker for intravascular hemolysis. The results are based on the LDH Total measurement. | |
| End point type | Secondary |
| End point timeframe: | |
| Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[7] | 3 ^[8] | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 60 (± 107) | 0 (± 197) | | |
| Day 7 | 71 (± 101) | -6 (± 167) | | |
| Day 14 | 4 (± 100) | 689 (± 1142) | | |
| Day 28 | 29 (± 110) | -69 (± 91) | | |

Notes:

[7] - Day 1: n=11, Day 7: n=9, Day 14: n=8, Day 28: n=8

[8] - Day 1: n=3, Day 7: n=3, Day 14: n=2; Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin levels - Change from baseline

| | |
|------------------------|---|
| End point title | Hemoglobin levels - Change from baseline |
| End point description: | A clinical laboratory endpoint that reflects the amount of red blood cells present in the blood. |
| End point type | Secondary |
| End point timeframe: | Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline, Day 1, Day 4, Day 7, Day 14, Day 28. |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[9] | 3 ^[10] | | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 0 (± 5) | -3 (± 7) | | |
| Day 4 | 1 (± 7) | 3 (± 3) | | |
| Day 7 | -1 (± 5) | 3 (± 2) | | |
| Day 14 | -2 (± 5) | -6 (± 1) | | |
| Day 28 | 0 (± 4) | -2 (± 5) | | |

Notes:

[9] - Day 1: n=11, Day 4: n=10, Day 7: n=10, Day 14: n=8, Day 28: n=10

[10] - Day 1: n=3, Day 4: n=3, Day 7: n=3, Day 14: n=2, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Direct bilirubin - Change from baseline

| | |
|-----------------|---|
| End point title | Direct bilirubin - Change from baseline |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline, Day 1, Day 4, Day 7, Day 14, Day 28.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[11] | 3 ^[12] | | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 0 (± 0) | 0 (± 0) | | |
| Day 4 | 0 (± 0) | 0 (± 0) | | |
| Day 7 | 0 (± 0) | 0 (± 0) | | |
| Day 14 | 0 (± 0) | 0 (± 0) | | |
| Day 28 | 0 (± 0) | 0 (± 0) | | |

Notes:

[11] - Day 1: n=11, Day 4: n=10, Day 7: n=10, Day 14: n=8, Day 28: n=10

[12] - Day 1: n=3, Day 4: n=3, Day 7: n=3, Day 14: n=2, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight - Change from baseline

| | |
|-----------------|------------------------------------|
| End point title | Body weight - Change from baseline |
|-----------------|------------------------------------|

End point description:

A negative change in body weight denotes a weight decrease, a positive change in body weight denotes a weight increase.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline, Day 1, Day 4, Day 7, Day 14, Day 21, Day 28.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[13] | 3 ^[14] | | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | -0.2 (± 0.7) | -0.6 (± 0.4) | | |
| Day 4 | -0.3 (± 1.6) | -0.4 (± 0.8) | | |
| Day 7 | -0.5 (± 1.6) | -0.7 (± 1.3) | | |
| Day 14 | 1.1 (± 0.8) | 0.8 (± 0.7) | | |

| | | | | |
|--------|-------------|-------------|--|--|
| Day 21 | 0.1 (± 1.4) | 0.5 (± 0.1) | | |
| Day 28 | 0.6 (± 0.9) | 0.4 (± 0.4) | | |

Notes:

[13] - Day 1: n=11, Day 4: n=10, Day 7: n=10, Day 14: n=8, Day 21: n=6, Day 28: n=10

[14] - Day 1: n=3, Day 4: n=3, Day 7: n=3, Day 14: n=2, Day 21: n=2, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise Tolerance: 6-Minute Walk Distance during the double-blind treatment period - Change from baseline

| | |
|-----------------|--|
| End point title | Exercise Tolerance: 6-Minute Walk Distance during the double-blind treatment period - Change from baseline |
|-----------------|--|

End point description:

Functional exercise capacity was evaluated by using the 6-minute walk test (6MWT) which measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. Guidelines developed by the American Thoracic Society were used for conducting the test and interpreting the results.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured prior to, during and after the end of dosing in the double-blind treatment period, ie, at baseline (= most recent value obtained prior to the start of dosing on Day 1), Day 4, Day 7, Day 14, and Day 28.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[15] | 3 ^[16] | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 4 | -8.5 (± 38.2) | 20.6 (± 8) | | |
| Day 7 | 36.9 (± 44.6) | 28.3 (± 24.3) | | |
| Day 14 | -0.1 (± 31.5) | 4.1 (± 6.1) | | |
| Day 28 | -14.9 (± 41.2) | -8.2 (± 8.2) | | |

Notes:

[15] - Day 4: n=9, Day 7: n=9, Day 14: n=8, Day 28: n=8

[16] - Day 4: n=3, Day 7: n=3, Day 14: n=2, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise Tolerance: 6-Minute Walk Distance on Day 49 of the post-treatment observation period - Change from baseline

| | |
|-----------------|--|
| End point title | Exercise Tolerance: 6-Minute Walk Distance on Day 49 of the post-treatment observation period - Change from baseline |
|-----------------|--|

End point description:

Functional exercise capacity was evaluated by using the 6-minute walk test (6MWT) which measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. Guidelines developed by the American Thoracic Society were used for conducting the test and interpreting the results.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Measured prior to dosing at baseline (= most recent value obtained prior to the start of dosing on Day 1) and on Day 49 of the post-treatment observation period. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 2 | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | -20.6 (± 41.3) | -1.1 (± 3.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise Tolerance: 6-Minute Walk Distance on Day 49 of the post-treatment observation period - Change from last day of double-blind treatment period (Day 28)

| | |
|-----------------|--|
| End point title | Exercise Tolerance: 6-Minute Walk Distance on Day 49 of the post-treatment observation period - Change from last day of double-blind treatment period (Day 28) |
|-----------------|--|

End point description:

Functional exercise capacity was evaluated by using the 6-minute walk test (6MWT) which measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. Guidelines developed by the American Thoracic Society were used for conducting the test and interpreting the results.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured on last day of double-blind treatment period (Day 28) and on Day 49 of the post-treatment observation period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 2 | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | -5.6 (± 63.6) | 7.2 (± 4.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the double-blind treatment period - Change from baseline

| | |
|--|---|
| End point title | Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the double-blind treatment period - Change from baseline |
| End point description: | |
| Subjects assessed their pain levels by using the 0-10 Numeric Rating Scale: | |
| 0 = No pain | |
| 1-3 = Mild pain (nagging, annoying, interfering little with activities of daily living [ADLs]) | |
| 4-6 = Moderate pain (interferes significantly with ADLs) | |
| 7-10 = Severe pain (disabling; unable to perform ADLs) | |
| A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain. Baseline was defined as the average of all measures taken from screening through the period prior to start of dosing on Day 1. Area under the curve (AUC) was computed using change from baseline in weekly average values at Day 7, Day 14, Day 21, and Day 28. | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects assessed and recorded their pain level daily. Weekly averages were calculated for the Day 7, Day 14, Day 21, and Day 28 assessments. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 ^[17] | 3 ^[18] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | 1.682 (± 3.482) | 4.533 (± 4.536) | | |
| Day 14 | -0.85 (± 1.255) | -0.65 (± 0.071) | | |
| Day 21 | -0.825 (± 1.302) | -0.65 (± 0.071) | | |
| Day 28 | -0.689 (± 1.279) | -0.65 (± 0.071) | | |
| Area under the curve (AUC) | -2.352 (± 2.674) | -3.229 (± 2.847) | | |

Notes:

[17] - Day 7: n=11, Day 14: n=10, Day 21: n=8, Day 28: n=9, AUC: n=11

[18] - Day 7: n=3, Day 14: n=2, Day 21: n=2, Day 28: n=2, AUC: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the post-treatment observation period - Change from baseline

| | |
|--|---|
| End point title | Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the post-treatment observation period - Change from baseline |
| End point description: | |
| Subjects assessed their pain levels by using the 0-10 Numeric Rating Scale: | |
| 0 = No pain | |
| 1-3 = Mild pain (nagging, annoying, interfering little with activities of daily living [ADLs]) | |
| 4-6 = Moderate pain (interferes significantly with ADLs) | |
| 7-10 = Severe pain (disabling; unable to perform ADLs) | |
| A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain. Baseline was defined as the average of all measures taken from screening through the period prior to start of dosing on Day 1. Area under the curve (AUC) was computed using change from baseline in | |

weekly average values at Day 7, Day 14, Day 21, Day 28, Day 35, Day 42 and Day 49.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Subjects assessed and recorded their pain level daily. Weekly averages were calculated for the Day 35, Day 42 and Day 49 assessments. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[19] | 2 ^[20] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 35 | -4.675 (± 3.729) | -7.75 (± 1.202) | | |
| Day 42 | -2.83 (± 5.494) | -7.75 (± 1.202) | | |
| Day 49 | -3.089 (± 6.049) | -8.15 (± 0.212) | | |
| Area under the curve (AUC) | -2.836 (± 3.637) | -6.118 (± 0.874) | | |

Notes:

[19] - Day 35: n=8, Day 42: n=10, Day 49: n=9, AUC: n=10

[20] - Day 35: n=2, Day 42: n=2, Day 49: n=2, AUC: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the post-treatment observation period - Change from last day of double-blind treatment period (Day 28)

| | |
|-----------------|---|
| End point title | Numerical Pain Rating Scale (NPRS): Worst pain (weekly average) in the post-treatment observation period - Change from last day of double-blind treatment period (Day 28) |
|-----------------|---|

End point description:

Subjects assessed their pain levels by using the 0-10 Numeric Rating Scale:

0 = No pain

1-3 = Mild pain (nagging, annoying, interfering little with activities of daily living [ADLs])

4-6 = Moderate pain (interferes significantly with ADLs)

7-10 = Severe pain (disabling; unable to perform ADLs)

A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain. Baseline was defined as the most recent value obtained on the last day of the double-blind dosing period (Day 28). Area under the curve (AUC) was computed using change from baseline (Day 28) in weekly average values at Day 35, Day 42 and Day 49.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Subjects assessed and recorded their pain level daily. Weekly averages were calculated for the Day 35, Day 42 and Day 49 assessments. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[21] | 2 ^[22] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 35 | -3.425 (± 3.302) | -7.75 (± 1.202) | | |
| Day 42 | -1.83 (± 4.905) | -7.75 (± 1.202) | | |
| Day 49 | -1.978 (± 5.479) | -8.15 (± 0.212) | | |
| AUC | -2.836 (± 3.637) | -6.118 (± 0.874) | | |

Notes:

[21] - Day 35: n=8, Day 42: n=10, Day 49: n=9, AUC: n=10

[22] - Day 35: n=2, Day 42: n=2, Day 49: n=2, AUC: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI): Average pain level in last 24 hours (double-blind treatment period) - Change from baseline

| | |
|-----------------|--|
| End point title | Brief Pain Inventory (BPI): Average pain level in last 24 hours (double-blind treatment period) - Change from baseline |
|-----------------|--|

End point description:

Subjects rated the severity of their pain by using the BPI short form. Pain was rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline (= the most recent value obtained prior to the start of the dosing on Day 1 of the double-blind dosing period) and on Days 7 and 28 of the double-blind treatment period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[23] | 3 ^[24] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | -0.4 (± 2.3) | -3 (± 3.3) | | |
| Day 28 | -0.6 (± 1.2) | -1.3 (± 3.2) | | |

Notes:

[23] - Day 7: n=10, Day 28: n=8

[24] - Day 7: n=3, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI): Worst pain level in last 24 hours (double-blind treatment period) - Change from baseline

| | |
|-----------------|---|
| End point title | Brief Pain Inventory (BPI): Worst pain level in last 24 hours |
|-----------------|---|

End point description:

Subjects rated the severity of their pain by using the BPI short form. Pain was rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline (= the most recent value obtained prior to the start of the dosing on Day 1 of the double-blind dosing period) and on Days 7 and 28 of the double-blind treatment period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[25] | 3 ^[26] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | -1 (± 3) | 0 (± 0) | | |
| Day 28 | -1 (± 3) | 1 (± 1) | | |

Notes:

[25] - Day 7: n=10, Day 28: n=8

[26] - Day 7: n=3, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI): Worst pain level in last 24 hours (post-treatment observation period) - Change from baseline

| | |
|-----------------|--|
| End point title | Brief Pain Inventory (BPI): Worst pain level in last 24 hours (post-treatment observation period) - Change from baseline |
|-----------------|--|

End point description:

Subjects rated the severity of their pain by using the BPI short form. Pain was rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). A negative mean change denotes a pain decrease. A positive mean change denotes an increase in pain.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline (= the most recent value obtained prior to the start of the dosing on Day 1 of the double-blind dosing period) and Day 49 of the post-treatment observation period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 2 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -1 (± 5) | 0 (± 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI): Interference of pain with aspects of life (general activity) during double-blind treatment period - Change from baseline

| | |
|-----------------|--|
| End point title | Brief Pain Inventory (BPI): Interference of pain with aspects of life (general activity) during double-blind treatment period - Change from baseline |
|-----------------|--|

End point description:

Subjects rated the degree to which their pain interfered with various daily functions by using the BPI short form. Interference with general activity was rated on a scale from 0 (does not interfere) to 10 (completely interferes).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline (= the most recent value obtained prior to the start of the dosing on Day 1 of the double-blind dosing period) and on Days 7 and 28 of the double-blind treatment period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[27] | 3 ^[28] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | 0 (± 2) | 0 (± 0) | | |
| Day 28 | 1 (± 2) | 0 (± 0) | | |

Notes:

[27] - Day 7: n=10, Day 28: n=8

[28] - Day 7: n=3, Day 28: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI): Interference of pain with aspects of life (general activity) during post-treatment observation period - Change from baseline

| | |
|-----------------|--|
| End point title | Brief Pain Inventory (BPI): Interference of pain with aspects of life (general activity) during post-treatment observation period - Change from baseline |
|-----------------|--|

End point description:

Subjects rated the degree to which their pain interfered with various daily functions by using the BPI short form. Interference with general activity was rated on a scale from 0 (does not interfere) to 10 (completely interferes).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At baseline (= the most recent value obtained prior to the start of the dosing on Day 1 of the double-blind dosing period) and on Day 49 of the post-treatment observation period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 2 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 0 (± 1) | 0 (± 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patients´ Global Impression of Change (PGIC) during the double-blind treatment period - Change from baseline

| | |
|-----------------|--|
| End point title | Patients´ Global Impression of Change (PGIC) during the double-blind treatment period - Change from baseline |
|-----------------|--|

End point description:

Subjects assessed the change in activity limitations, symptoms, emotions, and overall quality of life by using the 1- to 7-point PGIC scale. The question and scale was as follows: Since beginning treatment at this clinic, how would you describe the change in your sickle cell condition? Please circle the number that matches your overall judgment.

-3 - much worse

-2 - moderately worse

-1 - minimally worse

0 - no change

+1 - minimally improved

+2 - moderately improved

+3 - much improved

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

PGIC was measured at baseline and once weekly on Days 7, 14, 21, and 28. Baseline was defined as the most recent value obtained prior to the start of dosing on Day 1 of the double-blind treatment period.

No values available for placebo group for Day 28.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[29] | 3 ^[30] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | 0 (± 1) | 0 (± 0) | | |
| Day 14 | 0 (± 0) | 0 (± 0) | | |
| Day 21 | 0 (± 1) | 0 (± 0) | | |

Notes:

[29] - Day 7: n=10, Day 14: n=9, Day 21: n=8, Day 28: n=9

[30] - Day 7: n=3, Day 14: n=2, Day 21: n=2, Day 28: n=1

Statistical analyses

No statistical analyses for this end point

Secondary: Patients´ Global Impression of Change (PGIC) during the post-treatment observation period - Change from baseline

| | |
|---|--|
| End point title | Patients´ Global Impression of Change (PGIC) during the post-treatment observation period - Change from baseline |
| End point description: | |
| Subjects assessed the change in activity limitations, symptoms, emotions, and overall quality of life by using the 1- to 7-point PGIC scale. The question and scale was as follows: Since beginning treatment at this clinic, how would you describe the change in your sickle cell condition? Please circle the number that matches your overall judgment. | |
| -3 - much worse | |
| -2 - moderately worse | |
| -1 - minimally worse | |
| 0 - no change | |
| +1 - minimally improved | |
| +2 - moderately improved | |
| +3 - much improved | |
| End point type | Secondary |
| End point timeframe: | |
| PGIC was measured at baseline and once weekly in the post-treatment observation period on Days 35, 42, and 49. Baseline was defined as the most recent value obtained prior to the start of dosing on Day 1 of the double-blind treatment period. | |

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[31] | 2 ^[32] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 35 | 0 (± 1) | 0 (± 0) | | |
| Day 42 | 0 (± 1) | 0 (± 0) | | |
| Day 49 | 0 (± 1) | 0 (± 0) | | |

Notes:

[31] - Day 35: n=8, Day 42: n=10, Day 49: n=8

[32] - Day 35: n=2, Day 42: n=2, Day 49: n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Patients´ Global Impression of Change (PGIC) during the post-treatment observation period - Change from last day of double-blind treatment period

| | |
|---|---|
| End point title | Patients´ Global Impression of Change (PGIC) during the post-treatment observation period - Change from last day of double-blind treatment period |
| End point description: | |
| Subjects assessed the change in activity limitations, symptoms, emotions, and overall quality of life by using the 1- to 7-point PGIC scale. The question and scale was as follows: Since beginning treatment at this clinic, how would you describe the change in your sickle cell condition? Please circle the number that matches your overall judgment. | |
| -3 - much worse | |
| -2 - moderately worse | |
| -1 - minimally worse | |
| 0 - no change | |
| +1 - minimally improved | |
| +2 - moderately improved | |
| +3 - much improved | |
| End point type | Secondary |

End point timeframe:

PGIC was measured at baseline, once weekly during double-blind treatment and on Days 35, 42, and 49 of the post-treatment observation period. Baseline was defined as the most recent value obtained on the last day of the double-blind treatment period.

| End point values | Study Drug | Placebo | | |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[33] | 2 ^[34] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 35 | 0 (± 0) | 0 (± 0) | | |
| Day 42 | 0 (± 0) | 0 (± 0) | | |
| Day 49 | 0 (± 0) | 0 (± 0) | | |

Notes:

[33] - Day 35: n=8, Day 42: n=10, Day 49: n=8

[34] - Day 35: n=2, Day 42: n=2, Day 49: n=2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 9 weeks

Adverse event reporting additional description:

Adverse events, including sickle-cell specific symptoms, were to be monitored throughout the study, beginning from the time the subject is administered the first dose at the start of the outpatient placebo lead-in period through the final clinical visit, for a total of approximately 9 weeks.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|-----|
| Dictionary version | N/A |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo lead-in period (Day -14 to Day -1) |
|-----------------------|--|

Reporting group description:

Subjects who received at least 1 dose of placebo in the lead-in period, ie, prior to the double-blind treatment period; n=23, time frame: 2 weeks

| | |
|-----------------------|---|
| Reporting group title | Double-blind treatment period (Day 1 to Day 28) |
|-----------------------|---|

Reporting group description:

Subjects treated in the double-blind treatment period, (ie, randomized to study drug or placebo); n=14, time frame: 4 weeks

| | |
|-----------------------|--|
| Reporting group title | Post-treatment observation period (Day 29 to Day 49) |
|-----------------------|--|

Reporting group description:

Subjects who completed the double-blind treatment period and entered the post-treatment observation period; n=12, time frame: 3 weeks

| Serious adverse events | Placebo lead-in period (Day -14 to Day -1) | Double-blind treatment period (Day 1 to Day 28) | Post-treatment observation period (Day 29 to Day 49) |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 23 (8.70%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Sickle cell anaemia with crisis | | | |
| subjects affected / exposed | 2 / 23 (8.70%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sickle cell anaemia | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Placebo lead-in period (Day -14 to Day -1) | Double-blind treatment period (Day 1 to Day 28) | Post-treatment observation period (Day 29 to Day 49) |
|--|--|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 21 / 23 (91.30%) | 12 / 14 (85.71%) | 4 / 12 (33.33%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | 2 / 14 (14.29%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | 2 / 14 (14.29%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Investigations | | | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Transaminases increased | | | |

| | | | |
|---|---|--|---|
| subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 12 (0.00%) 0 |
| Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 12 (0.00%) 0 |
| Congenital, familial and genetic disorders Sickle cell anaemia subjects affected / exposed occurrences (all) | 5 / 23 (21.74%) 5 | 5 / 14 (35.71%) 6 | 2 / 12 (16.67%) 2 |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 12 (0.00%) 0 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) | 13 / 23 (56.52%) 13 5 / 23 (21.74%) 6 1 / 23 (4.35%) 1 | 1 / 14 (7.14%) 1 6 / 14 (42.86%) 6 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 2 |
| Eye disorders Diplopia subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain | 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 | 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 23 (0.00%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 23 (8.70%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Faeces discoloured | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 23 (13.04%) | 4 / 14 (28.57%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 23 (4.35%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal stiffness | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 23 (8.70%) 2 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 12 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 2 / 14 (14.29%) 2 | 0 / 12 (0.00%) 0 |
| Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all) | 2 / 23 (8.70%) 2 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| The study was put on hold (before completion of Cohort A) due to problems with the PK assay which rendered all PK data invalid, before being closed by the sponsor due to unblinding of the subject, site and sponsor to study drug and placebo treatment. |
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Notes: