



## 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
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##### 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
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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
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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 <sup>[1]</sup>	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
<b>Arm title</b>	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

<b>Arm title</b>	Placebo
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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
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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

<b>Number of subjects in period 2</b>	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
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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)
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Subject analysis set type	Full analysis
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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)
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Subject analysis set type	Sub-group analysis
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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)
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Subject analysis set type	Sub-group analysis
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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)
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Subject analysis set type	Safety analysis
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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		

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## 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) <sup>[1]</sup>
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) <sup>[2]</sup>
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End point description:

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

End point type	Primary
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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) <sup>[3]</sup>
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End point description:

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

End point type	Primary
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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 <sup>[4]</sup>
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End point description:

End point type	Primary
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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
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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
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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
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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
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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
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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
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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 <sup>[5]</sup>	3 <sup>[6]</sup>		
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 <sup>[7]</sup>	3 <sup>[8]</sup>		
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 <sup>[9]</sup>	3 <sup>[10]</sup>		
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
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End point description:

End point type	Secondary
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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 <sup>[11]</sup>	3 <sup>[12]</sup>		
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
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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
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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 <sup>[13]</sup>	3 <sup>[14]</sup>		
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
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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
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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 <sup>[15]</sup>	3 <sup>[16]</sup>		
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
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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)
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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 <sup>[17]</sup>	3 <sup>[18]</sup>		
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 <sup>[19]</sup>	2 <sup>[20]</sup>		
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)
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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 <sup>[21]</sup>	2 <sup>[22]</sup>		
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
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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
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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 <sup>[23]</sup>	3 <sup>[24]</sup>		
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
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## 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
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## 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 <sup>[25]</sup>	3 <sup>[26]</sup>		
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
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## 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
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## 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

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

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

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End point values	Study Drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[27]</sup>	3 <sup>[28]</sup>		
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

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**Statistical analyses**

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No statistical analyses for this end point

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

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

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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
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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
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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 <sup>[29]</sup>	3 <sup>[30]</sup>		
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 <sup>[31]</sup>	2 <sup>[32]</sup>		
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

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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.

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End point values	Study Drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[33]</sup>	2 <sup>[34]</sup>		
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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	N/A
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### Reporting groups

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

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

<b>Serious adverse events</b>	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 %

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



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

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: