



## Clinical trial results:

### A Phase I/II Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of the -Hemoglobinopathies (Sickle Cell Disease and -Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral -A-T87Q-Globin Vector (LentiGlobin® BB305 Drug Product)

#### Summary

EudraCT number	2012-000695-42
Trial protocol	FR
Global end of trial date	26 February 2019

#### Results information

Result version number	v1 (current)
This version publication date	07 September 2019
First version publication date	07 September 2019

#### Trial information

##### Trial identification

Sponsor protocol code	HGB-205
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02151526
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	bluebird bio, Inc
Sponsor organisation address	60 Binney Street, Cambridge, Massachusetts, United States, 02142
Public contact	Study Medical Director, bluebird bio. Inc, +31 30 310 04 50, medinfo@bluebirdbio.com
Scientific contact	Study Medical Director, bluebird bio. Inc, +31 30 310 04 50, medinfo@bluebirdbio.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001665-PIP02-17
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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2019
Global end of trial reached?	Yes
Global end of trial date	26 February 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the safety, tolerability, and success of engraftment with LentiGlobin BB305 Drug Product after conditioning with Busilvex (busulfan IV) in subjects with severe sickle cell disease (SCD) or transfusion dependent  $\beta$ -thalassemia (TDT).

Protection of trial subjects:

All monitoring visits were conducted according to the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

PIP was available only for SCD subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	France: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	4
Adults (18-64 years)	3

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at a single site in France in between 07 June 2013 (First subject signed informed consent) to 26 February 2019 (Last subject last visit).

### Pre-assignment

Screening details:

A total of 7 subjects were enrolled and completed the study. 3 had Sickle Cell Disease (SCD) and 4 had transfusion-dependent  $\beta$ -thalassemia (TDT).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LentiGlobin BB305 Drug Product for SCD

Arm description:

Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 milligram per kilogram per day (mg/kg/day) busulfan intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of greater than or equal to ( $>$  or  $=$ )  $2.0 \times 10^6$  CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with sickle cell disease (SCD) by IV infusion.

Arm type	Experimental
Investigational medicinal product name	LentiGlobin BB305 Drug Product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

LentiGlobin BB305 drug product was administered by intravenous (IV) infusion.

<b>Arm title</b>	LentiGlobin BB305 Drug Product for TDT
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Arm description:

Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 mg/kg/day busulfan Intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of  $>$  or  $= 3.0 \times 10^6$  CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with transfusion-dependent  $\beta$ -thalassemia (TDT) by IV infusion.

Arm type	Experimental
Investigational medicinal product name	LentiGlobin BB305 Drug Product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

LentiGlobin BB305 drug product was administered by intravenous (IV) infusion.

<b>Number of subjects in period 1</b>	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT
Started	3	4
Completed	3	4

## Baseline characteristics

### Reporting groups

Reporting group title	LentiGlobin BB305 Drug Product for SCD
Reporting group description:	
Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 milligram per kilogram per day (mg/kg/day) busulfan intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of greater than or equal to ( $>$ or $=$ ) $2.0 \times 10^6$ CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with sickle cell disease (SCD) by IV infusion.	
Reporting group title	LentiGlobin BB305 Drug Product for TDT
Reporting group description:	
Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 mg/kg/day busulfan Intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of $>$ or $= 3.0 \times 10^6$ CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with transfusion-dependent $\beta$ -thalassemia (TDT) by IV infusion.	

Reporting group values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT	Total
Number of subjects	3	4	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	2	4
Adults (18-64 years)	1	2	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	2	4
Male	1	2	3

## End points

### End points reporting groups

Reporting group title	LentiGlobin BB305 Drug Product for SCD
Reporting group description:	
Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 milligram per kilogram per day (mg/kg/day) busulfan intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of greater than or equal to ( $>$ or $=$ ) $2.0 \times 10^6$ CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with sickle cell disease (SCD) by IV infusion.	
Reporting group title	LentiGlobin BB305 Drug Product for TDT
Reporting group description:	
Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 mg/kg/day busulfan Intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of $>$ or $= 3.0 \times 10^6$ CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with transfusion-dependent $\beta$ -thalassemia (TDT) by IV infusion.	

### Primary: Number of Treated Subjects With Successful Neutrophil and Platelet Engraftment

End point title	Number of Treated Subjects With Successful Neutrophil and Platelet Engraftment <sup>[1]</sup>
End point description:	
Neutrophil engraftment was defined as the first of absolute neutrophil count (ANC) $>$ or $= 0.5 \times 10^9$ /liter (L) for 3 consecutive days (or 3 consecutive measurements done on separate days), after a post-transplant value less than [ $<$ ] $0.5 \times 10^9$ /L). Platelet engraftment was defined as the first of 3 consecutive platelet values $>$ or $= 20 \times 10^9$ /L for subjects with TDT and values $>$ or $= 50 \times 10^9$ /L for subjects with SCD obtained on different days with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. The day of engraftment is the first day of the 3 consecutive platelet measurements. This endpoint was evaluated in the Transplant Population (TP), which included all subjects in the intent-to-treat (ITT) population who underwent LentiGlobin BB305 Drug Product infusion.	
End point type	Primary
End point timeframe:	
From time of drug product infusion through Month 24 visit	

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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of Subjects				
Subjects with Neutrophil Engraftment	3	4		
Subjects with Platelet Engraftment	3	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to Successful Neutrophil and Platelet Engraftment

End point title	Time to Successful Neutrophil and Platelet Engraftment <sup>[2]</sup>
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End point description:

Neutrophil engraftment was defined as the first of ANC  $\geq 0.5 \times 10^9/\text{liter (L)}$  for 3 consecutive days (or 3 consecutive measurements done on separate days), after a post-transplant value  $< 0.5 \times 10^9/\text{L}$ . Platelet engraftment was defined as the first of 3 consecutive platelet values  $\geq 20 \times 10^9/\text{L}$  for subjects with TDT and values  $\geq 50 \times 10^9/\text{L}$  for subjects with SCD obtained on different days with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. The day of engraftment is the first day of the 3 consecutive platelet measurements. This endpoint was evaluated in the Transplant Population (TP).

End point type	Primary
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End point timeframe:

From time of drug product infusion through Month 24 visit

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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Days				
median (full range (min-max))				
Time to neutrophil engraftment	32 (27 to 38)	16.5 (14 to 29)		
Time to platelet engraftment	51 (39 to 92)	23 (20 to 26)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Incidence of Transplant Related Mortality

End point title	Incidence of Transplant Related Mortality <sup>[3]</sup>
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End point description:

This is the safety endpoint related to mortality. Transplant related mortality was defined as any death occurring in the study post drug product infusion deemed related to the transplant by the investigator. This endpoint was evaluated in the Transplant Population (TP).

End point type	Primary
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End point timeframe:

From screening through 365 days post-transplant

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: Descriptive statistics were performed; no inferential statistical analyses were performed.



End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of Subjects	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Overall Survival

End point title	Overall Survival <sup>[4]</sup>
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End point description:

Overall survival was defined as time from date of LentiGlobin BB305 Drug Product infusion (Day 1) to date of death. Overall survival was censored at the date of last visit if the subject was still alive. Subjects who survived throughout the study were reported in this endpoint. This endpoint was evaluated in the ITT population, which consisted of all subjects who initiated any study procedures, beginning with mobilization (by granulocyte-colony stimulating factor [G-CSF] with or without plerixafor), or bone marrow harvest.

End point type	Primary
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End point timeframe:

From time of drug product infusion through Month 24 visit

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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of Subjects	3	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Vector-Derived Replication-Competent Lentivirus (RCL)

End point title	Percentage of Subjects With Vector-Derived Replication-Competent Lentivirus (RCL) <sup>[5]</sup>
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End point description:

Blood samples were analyzed for detection of RCL using RCL co-culture assay. This endpoint was evaluated in the ITT population.

End point type	Primary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[5] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Percentage of subjects				
number (not applicable)	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Treated Subjects With (>) 30 Percent (%) Contribution of an Individual Clone As Per Integration Site Analysis (ISA)

End point title	Number of Treated Subjects With (>) 30 Percent (%) Contribution of an Individual Clone As Per Integration Site Analysis (ISA) <sup>[6]</sup>
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End point description:

Clonal dominance was defined as an ISA result greater than (>) 90% of the total IS at any time and a vector copy number (VCN) > or =0.3, or an initial ISA result of > 30% of the total IS with a VCN > or =0.3 followed by a result > 30% and less than or equal to (< or =)90% at first repeat and a result > 50% at second repeat. This endpoint was evaluated in the Transplant Population (TP).

End point type	Primary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[6] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of Subjects	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious
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## End point description:

An AE was any untoward medical occurrence associated with the use of a drug in subjects, whether or not considered drug related. An AE may include a change in physical signs, symptoms, and/or clinically significant laboratory change occurring in any phase of a clinical study. This definition includes inter-current illnesses or injuries, and exacerbation of pre-existing conditions. An SAE was any AE, occurring at any dose and regardless of causality, that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or was considered an important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent an outcome listed previously. The number of subjects with AEs and SAEs was evaluated. This endpoint was evaluated in the ITT population.

End point type	Primary
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## End point timeframe:

From date of Informed Consent up to Month 24 visit

## Notes:

[7] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of Subjects				
Number of Subjects with any Adverse Event	3	4		
Number of Subjects with any Serious Adverse Event	3	3		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Treated TDT Subjects Who Achieved Transfusion independence (TI)

End point title	Percentage of Treated TDT Subjects Who Achieved Transfusion independence (TI) <sup>[8]</sup>
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## End point description:

TI was defined as a weighted average hemoglobin (Hb) > or =9 grams per deciliter (g/dL) without any pRBC transfusions for a continuous period of > or =12 months at any time during the study after drug product infusion, where calculation of time period of TI starts when subjects achieve a Hb > or =9 g/dL with no transfusions in the preceding 60 days. This endpoint was evaluated in the TDT Transplant Population (TP).

End point type	Secondary
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## End point timeframe:

From time of drug product infusion through Month 24 visit

## Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Transfusion Independence (TI) was only evaluated in TDT subjects.

<b>End point values</b>	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Percentage of subjects				
number (not applicable)	75			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Weighted Average Hemoglobin (Hb) During Period of Transfusion Independence (TI)

End point title	Weighted Average Hemoglobin (Hb) During Period of Transfusion Independence (TI) <sup>[9]</sup>
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End point description:

TI was defined as a weighted average hemoglobin (Hb) > or =9 grams per deciliter (g/dL) without any pRBC transfusions for a continuous period of > or =12 months at any time during the study after drug product infusion, where calculation of time period of TI starts when subjects achieve a Hb > or =9 g/dL with no transfusions in the preceding 60 days. This endpoint was evaluated in the TDT Transplant Population (TP) that reached TI.

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Transfusion Independence (TI) was only evaluated in TDT subjects.

<b>End point values</b>	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: grams per deciliter				
median (full range (min-max))	11.3 (10.6 to 13.1)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Transfusion Independence (TI)

End point title	Duration of Transfusion Independence (TI) <sup>[10]</sup>
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End point description:

TI was defined as a weighted average Hb > or =9 grams per deciliter (g/dL) without any pRBC transfusions for a continuous period of > or =12 months at any time during the study after drug product

infusion, where calculation of time period of TI starts when subjects achieve a Hb > or =9 g/dL with no transfusions in the preceding 60 days. To meet the initial TI criteria, the weighted Hb must be > or =9 g/dL at the end of the 12-month period, to remain in the TI state beyond the 12-month period, the treated subject needs to maintain a weighted Hb of > or =9 g/dL from that point forward, without receiving a pRBC transfusion. This endpoint reports the duration of TI and was evaluated in the TDT Transplant Population (TP) that reached TI.

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Transfusion Independence (TI) was only evaluated in TDT subjects.

<b>End point values</b>	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Month				
median (full range (min-max))	21.7 (21.2 to 21.8)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time From LentiGlobin BB305 Drug Product Infusion to Last Packed Red Blood Cells (pRBC) Transfusion Prior to Achieving Transfusion Independence (TI)

End point title	Time From LentiGlobin BB305 Drug Product Infusion to Last Packed Red Blood Cells (pRBC) Transfusion Prior to Achieving Transfusion Independence (TI) <sup>[11]</sup>
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End point description:

TI was defined as a weighted average Hb > or =9 grams per deciliter (g/dL) without any pRBC transfusions for a continuous period of > or =12 months at any time during the study after drug product infusion, where calculation of time period of TI starts when subjects achieve a Hb > or =9 g/dL with no transfusions in the preceding 60 days. To meet the initial TI criteria, the weighted Hb must be > or =9 g/dL at the end of the 12-month period, to remain in the TI state beyond the 12-month period, the treated subject needs to maintain a weighted Hb of > or =9 g/dL from that point forward, without receiving a pRBC transfusion. This endpoint reports the time from infusion to the last pRBC transfusion prior to achieving TI and was evaluated in the TDT Transplant Population (TP) that reached TI.

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Transfusion Independence (TI) was only evaluated in TDT subjects.

<b>End point values</b>	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Days				
median (full range (min-max))	11 (5 to 13)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time from LentiGlobin BB305 Drug Product Infusion to Achieving Transfusion Independence (TI)

End point title	Time from LentiGlobin BB305 Drug Product Infusion to Achieving Transfusion Independence (TI) <sup>[12]</sup>
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End point description:

TI was defined as a weighted average Hb > or =9 grams per deciliter (g/dL) without any pRBC transfusions for a continuous period of > or =12 months at any time during the study after drug product infusion, where calculation of time period of TI starts when subjects achieve a Hb > or =9 g/dL with no transfusions in the preceding 60 days. To meet the initial TI criteria, the weighted Hb must be > or =9 g/dL at the end of the 12-month period, to remain in the TI state beyond the 12-month period, the treated subject needs to maintain a weighted Hb of > or =9 g/dL from that point forward, without receiving a pRBC transfusion. This endpoint reports the time from infusion to achievement of TI and was reported in the TDT Transplant Population (TP) that reached TI.

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Transfusion Independence (TI) was only evaluated in TDT subjects.

<b>End point values</b>	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Month				
median (full range (min-max))	14.9 (14.9 to 15.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Weighted Average Nadir Hemoglobin (Hb)

End point title	Weighted Average Nadir Hemoglobin (Hb) <sup>[13]</sup>
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End point description:

Weighted average Hb nadir was defined as an average area under the curve where the Hb closest but within 3 days prior to a transfusion was used as the Hb nadir. Hb values on the day of the transfusion were considered for nadir calculations. This endpoint was evaluated in the TDT Transplant Population (TP).

End point type	Secondary
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End point timeframe:

From 6 months post-drug product infusion through Month 24 visit

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Weighted Average Nadir Hemoglobin (Hb) was evaluated only in TDT subjects.

End point values	LentiGlobin BB305 Drug Product for TDT			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: grams per deciliter (g/dL)				
median (full range (min-max))	11 (8.5 to 13.2)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Change From Baseline in Annualized Packed Red Blood Cell (pRBC) Transfusion Volume

End point title	Percentage Change From Baseline in Annualized Packed Red Blood Cell (pRBC) Transfusion Volume
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End point description:

Percent change from baseline in the average annual transfusion volume from 6 months post-drug product infusion through last visit were reported. This endpoint was evaluated in the Transplant Population (TP).

End point type	Secondary
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End point timeframe:

Baseline, From 6 months post-drug product infusion through Month 24 visit

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percent change in Annualized pRBC volume				
median (full range (min-max))	-100.0 (-100.0 to 90.0)	-100.0 (-100.0 to -100.0)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline in Annualized Number of Packed Red Blood Cell (pRBC) Transfusions

End point title	Percentage Change From Baseline in Annualized Number of Packed Red Blood Cell (pRBC) Transfusions
End point description: Frequency of pRBC transfusions (number per year) from 6 months post-drug product infusion through last visit were reported. This endpoint was evaluated in the Transplant Population (TP).	
End point type	Secondary
End point timeframe: Baseline, From 6 months post-drug product infusion through Month 24 visit	

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percentage change in pRBC transfusion				
median (full range (min-max))	-100.0 (-100.0 to -1.9)	-100.0 (-100.0 to -100.0)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Vaso-Occlusive Crisis (VOC) and/or Acute Chest Syndrome (ACS) Events Post Drug Product Infusion

End point title	Number of Subjects with Vaso-Occlusive Crisis (VOC) and/or Acute Chest Syndrome (ACS) Events Post Drug Product Infusion <sup>[14]</sup>
End point description: Number of VOCs, ACS, and vaso-occlusive events (VOEs; which included both VOC and ACS) through 24 months after drug product infusion, compared to 2 years prior to enrollment. This endpoint was evaluated in ITT population.	
End point type	Secondary
End point timeframe: From time of drug product infusion through Month 24 visit	



Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: VOC and/or ACS events were only evaluable in SCD subjects

End point values	LentiGlobin BB305 Drug Product for SCD			
Subject group type	Reporting group			
Number of subjects analysed	3 <sup>[15]</sup>			
Units: Number of Subjects				
Vaso-Occlusive Crisis (VOC)	1			
Acute Chest Syndrome (ACS)	1			

Notes:

[15] - Events of VOC and ACS were from same subject

## Statistical analyses

No statistical analyses for this end point

## Secondary: Therapeutic Globin Expression Measured by Hb Containing $\beta^A$ -T87Q Globin (HbA<sup>T87Q</sup>) in Peripheral Blood

End point title	Therapeutic Globin Expression Measured by Hb Containing $\beta^A$ -T87Q Globin (HbA <sup>T87Q</sup> ) in Peripheral Blood
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End point description:

Therapeutic globin expression was measured by HbA<sup>T87Q</sup> in peripheral blood and the ratio of alpha( $\alpha$ )-globin to all beta ( $\beta$ )-like-globins. The relative amount of each globin produced by a subject (including  $\beta^A$ -T87Q globin) was determined in peripheral blood throughout the study. This endpoint was evaluated in the Transplant Population (TP).

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: gram/deciliter (g/dL)				
arithmetic mean (standard deviation)	2.947 ( $\pm$ 2.4415)	8.287 ( $\pm$ 1.5758)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vector Copy Number (VCN) in Peripheral Blood

End point title	Vector Copy Number (VCN) in Peripheral Blood
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End point description:

LentiGlobin BB305 lentiviral vector (LVV) transduction efficiency was measured by VCN. The presence of vector sequences in the genomic DNA of cells is detected using quantitative polymerase chain reaction (qPCR), and results were expressed as VCN. This endpoint was evaluated in the Transplant Population (TP).

End point type	Secondary
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End point timeframe:

From time of drug product infusion through Month 24 visit

End point values	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: copies per diploid genome (c/dg)				
arithmetic mean (standard deviation)	0.898 (± 1.1655)	1.796 (± 1.3665)		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of informed consent through Month 24 visit

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	LentiGlobin BB305 Drug Product for SCD
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Reporting group description:

Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 milligram per kilogram per day (mg/kg/day) busulfan intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of  $>$  or  $= 2.0 \times 10^6$  CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with SCD by IV infusion.

Reporting group title	LentiGlobin BB305 Drug Product for TDT
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Reporting group description:

Following myeloablative conditioning with a dose (dose may be adjusted as per protocol) of 3.2 mg/kg/day busulfan Intravenous (IV) for 4 consecutive days and subsequent daily monitoring of busulfan levels until no busulfan was detected, a single dose of greater than or equal to  $>$  or  $= 3.0 \times 10^6$  CD34+ cells/kg LentiGlobin BB305 Drug Product was administered to subjects with transfusion-dependent  $\beta$ -thalassemia (TDT) by IV infusion.

Serious adverse events	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 4 (75.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Presyncope			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	LentiGlobin BB305 Drug Product for SCD	LentiGlobin BB305 Drug Product for TDT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Xerosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Non-cardiac chest pain			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Puncture site pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	8	5	
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hypothermia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Injection site inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Premature menopause			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Lung disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Restrictive pulmonary disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Disturbance in attention			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)	3 / 4 (75.00%)	
occurrences (all)	3	4	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)	3 / 4 (75.00%)	
occurrences (all)	3	4	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Staphylococcus test positive			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Aspergillus test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Catheter site pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Dolichocolon			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Presyncope			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			



subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	3	4	
Neutropenia			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	4	4	
Anaemia			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	15	5	
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Sickle cell anaemia with crisis			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 3 (66.67%)	4 / 4 (100.00%)	
occurrences (all)	4	6	
Vomiting			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	
occurrences (all)	5	3	
Nausea			
subjects affected / exposed	3 / 3 (100.00%)	3 / 4 (75.00%)	
occurrences (all)	4	4	
Diarrhoea			
subjects affected / exposed	3 / 3 (100.00%)	3 / 4 (75.00%)	
occurrences (all)	4	3	
Stomatitis			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	3	7	
Anal fissure			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Lip dry			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Anal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
occurrences (all)	3	4	
Melanoderma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	2	2	

Pruritus generalised subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Skin hyperpigmentation subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Dry skin subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	
Petechiae subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	1 / 4 (25.00%) 1	
Bone pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2	0 / 4 (0.00%) 0	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Infections and infestations Folliculitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	
Bronchitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Genital candidiasis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Tooth abscess			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Wound infection fungal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Mastitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	1	3	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2012	Original: Enrollment in Study HGB 205 began.
05 October 2012	Version 2: Enrollment of subjects with severe SCD and cerebral vasculopathy was made contingent upon approval by ANSM, the Comité de protection des personnes (CPP), and the Comité de Surveillance (CDS) after review of safety and efficacy data from $\geq 2$ SCD subjects without cerebral vasculopathy treated with LentiGlobin BB305 Drug Product in this study. Hematologic abnormalities considered a direct consequence of the conditioning regimen were to be reported.
23 September 2013	Version 3: Clarified that approval for enrollment of subjects with severe SCD and cerebral vasculopathy is the jurisdiction of the Comité de Surveillance. Clarified that ovarian tissue grafting potentially may be offered to subjects under the context of biomedical research. Busulfan range corrected for units and dosing regimen (changed from 'range 800 to 1100 micrometer per minute ( $\mu\text{M}/\text{min}$ )' to 'Area Under Curve (AUC) range 800 to 1100 $\mu\text{M} \cdot \text{min}$ for a q6 hour dosing regimen, or 3200 to 4400 $\mu\text{M} \cdot \text{min}$ for a daily dosing regimen') Increased monitoring of physical examinations, CBCs, and vital signs during apheresis
07 July 2014	Version 4: Staggering altered from 3 subjects observed for 2 months to 2 subjects observed for 3 months, as longer observation of initial subjects felt to give more safety information than shorter observation of more subjects. Washout definition changed from "there must be a minimum of 4 busulfan washout days" to "until no busulfan is detected for at least 2 consecutive days", as considered sufficient for HSC safety.
15 December 2014	Version 5.1: Increased the frequency of HPLC globin analyses to provide better kinetics. Added erythropoietin tests, erythroblast counts, and exploratory bone marrow cellularity studies to help evaluate erythropoiesis; a new set of exploratory tests for sickle cell disease (SCD) to assist in evaluating the efficacy of treatment on this disease; new immunology testing to provide more safety data. Removed VCN and globin chain analysis in BFU Es in blood and bone marrow, as VCN in peripheral blood adequate to monitor persistence; removed RCL and ISA time points not recommended by regulatory authorities. Clarified that additional cell collection procedures may be allowed in the event of drug product release-testing failure.

26 August 2015	Version 6: The stipulation that safety and efficacy data from at least 2 SCD subjects without cerebral vasculopathy treated with LentiGlobin BB305 Drug Product be available in Study HGB-205 specifically was removed because bluebird bio has another ongoing study with LentiGlobin BB305 in subjects with severe SCD in the USA (Study HGB-206), and the required safety and efficacy data pre-specified to allow enrollment of SCD subjects with cerebral vasculopathy will be available collectively from the 2 ongoing studies (HGB-205 and HGB-206). The amount and duration of data required from these 2 trials to allow enrollment of SCD subjects with cerebral vasculopathies in this study remained at the discretion of the CDS.
19 May 2016	Version 7: Adjusted the acceptable busulfan range (from AUC 800 to 1100 $\mu\text{M}\cdot\text{min}$ to 1000 to 1300 $\mu\text{M}\cdot\text{min}$ for an every 6 hour dosing regimen, and from AUC 3200 to 4400 $\mu\text{M}\cdot\text{min}$ to 4000 to 5200 $\mu\text{M}\cdot\text{min}$ for a daily dosing regimen) based on clinical experience that increased busulfan exposure assists in achieving improved efficacy outcomes. Increased the minimum cell number for the dose from $1.5 \times 10^6$ CD34+ cells/kg to $2.0 \times 10^6$ CD34+ cells/kg when bone marrow is used as the cell source, as well as increased the number of bone marrow harvests that may be performed to up to 3 bone marrow harvests, based on clinical experience suggesting that doses above the current minimum may promote a better clinical response, and on acceptable clinical safety observed during bone marrow harvests in this study to date, for subjects with SCD.

Notes:

## 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.

PIP was available only for SCD subjects.

Notes: