Clinical trial results:
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent -Thalassemia, who do not have a 0/0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral A-T87Q-Globin Vector in Subjects 50 Years of Age

Summary

EudraCT number	2015-004122-33
Trial protocol	IT DE GR GB FR
Global end of trial date	31 March 2022

Results information

Result version number	v1 (current)
This version publication date	04 October 2022
First version publication date	04 October 2022

Trial information

Trial identification

Sponsor protocol code	HGB-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02906202
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bluebird bio, Inc.
Sponsor organisation address	455 Grand Union Blvd, Somerville, United States, MA 02145
Public contact	Clinical Trials Operations, bluebird bio, Inc., 001 3394999300, clinicaltrials@bluebirdbio.com
Scientific contact	Clinical Trials Operations, bluebird bio, Inc., 001 3394999300, clinicaltrials@bluebirdbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001665-PIP01-14
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	31 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study was to evaluate the efficacy of treatment with LentiGlobin BB305 Drug Product (betibeglogene autotemcel) in subjects less than or equal to (<=) 50 of age with transfusion-dependent β-thalassemia (TDT), who do not have β0/β0 genotype at the β-globin (HBB) gene.

Protection of trial subjects:

This study was performed in accordance with Title 21, United States (US) Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312 Subpart D; the International Council for Harmonisation (ICH) Guideline on Good Clinical Practice (GCP; E6); and the ethical principles outlined in the Declaration of Helsinki; and/or, where applicable, the European Directive 2001/20/EC relating to implementation of GCP in the conduct of clinical trials on medicinal products for human use and Directive 2005/28/EC on GCP for investigational medicinal products for human use.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	08 August 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	13 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	24
EEA total number of subjects	9

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)	8
Adolescents (12-17 years)	6
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 centers from 08 August 2016 to 31 March 2022.

Pre-assignment

Screening details:

A total of 24 subjects were enrolled, of which 23 subjects aged <= 50 years were treated of LentiGlobin BB305 Drug Product.

Period 1

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

Arms

Arm title	LentiGlobin BB305 Drug Product

Arm description:

Subjects <= 50 years of age received a single intravenous (IV) infusion of LentiGlobin BB305 Drug Product at a dose of >= 5.0 × 10^6 CD34+ cells/kilogram (kg) following myeloablative conditioning with busulfan (termed the Transplant population). As appropriate, data are analysed at times based on Intent-to-Treat (ITT) population which included all 24 subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.

Arm type	Experimental
Investigational medicinal product name	LentiGlobin BB305 Drug Product
Investigational medicinal product code	
Other name	betibeglogene autotemcel, beti-cel
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single IV infusion of >=5.0 x 10^6 CD34+ cells/kg of LentiGlobin BB305 Drug Product.

Number of subjects in period 1	LentiGlobin BB305 Drug Product
Started	24
Completed	23
Not completed	1
Discontinued after mobilization due to pregnancy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall study (overall period)
Reporting group description:	
Subjects <= 50 years of age received a single intravenous (IV) infusion of LentiGlobin BB305 Drug Product at a dose of >= 5.0 × 10^6 CD34+ cells/kilogram (kg) following myeloablative conditioning with busulfan (termed the Transplant population). As appropriate, data are analysed at times based on Intent-to-Treat (ITT) population which included all 24 subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.	

Reporting group values	Overall study (overall period)	Total	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	15.0		
full range (min-max)	4 to 34	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	11	11	
Race			
Units: Subjects			
Asian	14	14	
White	8	8	
Other	2	2	
American Indian or Alaska Native	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Not Provided	0	0	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	22	22	
Not Provided	1	1	

End points

End points reporting groups

Reporting group title	LentiGlobin BB305 Drug Product

Reporting group description:

Subjects <= 50 years of age received a single intravenous (IV) infusion of LentiGlobin BB305 Drug Product at a dose of >= 5.0 × 10^6 CD34+ cells/kilogram (kg) following myeloablative conditioning with busulfan (termed the Transplant population). As appropriate, data are analysed at times based on Intent-to-Treat (ITT) population which included all 24 subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.

Primary: Percentage of Subjects who Meet the Definition of Transfusion Independence (TI)

End point title	Percentage of Subjects who Meet the Definition of Transfusion Independence (TI)[1]

End point description:

TI was defined as a weighted average hemoglobin (Hb) >= 9 grams per deciliter (g/dL) without any packed red blood cell (pRBC) transfusions for a continuous period of >= 12 months at any time during the study after drug product infusion. Transplant Population (TP) included all subjects who received beti-cel. Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.

End point type	Primary

End point timeframe:

From 14 to 24 months post-transplant

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			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (confidence interval 95%)	91.3 (72.0 to 98.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Meet the Definition of Transfusion Independence (TI) at Month 24

End point title	Percentage of Subjects who Meet the Definition of Transfusion Independence (TI) at Month 24

End point description:

TI was defined as a weighted average hemoglobin (Hb) >= 9 grams per deciliter (g/dL) without any packed red blood cell (pRBC) transfusions for a continuous period of >= 12 months at any time during the study after drug product infusion. Percentage of subjects who met the definition of TI at Month 24 were evaluated. TP included all subjects who received beti-cel. Subjects evaluable for TI are defined as

subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.

End point type	Secondary

End point timeframe:

At Month 24 post-transplant

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (confidence interval 95%)	91.3 (72.0 to 98.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Transfusion Independence (TI)

End point title	Duration of Transfusion Independence (TI)

End point description:

Duration of TI was calculated as the time from the start of TI (i.e. first Hb >=9 with no transfusions in the preceding 60 days) up to the last available Hb at which the TI criteria are still met using Kaplan-Meier methodology. Duration of TI from start of TI up to Month 24 months was reported. TP included all subjects who received beti-cel. Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.

End point type	Secondary

End point timeframe:

From start of TI up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: months				
median (full range (min-max))	20.50 (18.2 to 22.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Drug Product Infusion to Achievement of Transfusion Independence (TI)

End point title	Time From Drug Product Infusion to Achievement of Transfusion Independence (TI)

End point description:

Time from drug product infusion to achievement of TI was calculated as the time from drug product infusion to the first hemoglobin at which a subject can be declared as TI (that is to 'start of TI + >= 12 months', dependent on Hb lab schedule). TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who achieved TI.

End point type	Secondary

End point timeframe:

From 14 months post-drug product infusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: months				
median (full range (min-max))	15.51 (14.8 to 19.4)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Weighted Average Hemoglobin (Hb) During Transfusion Independence (TI)

End point description:

Weighted Hb 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. Weighted average Hb during TI from 2 months post-drug product infusion through the Month 24 was reported. TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who achieved TI.

End point type	Secondary

End point timeframe:

From 60 days after the last pRBC transfusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: grams per deciliter (g/dL)				
arithmetic mean (standard deviation)	11.473 (± 1.0395)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who had a Reduction of At least 50%, 60%, 75%, 90% or 100% in the Annualized pRBCs Transfusion Volume

End point title	Percentage of Subjects who had a Reduction of At least 50%, 60%, 75%, 90% or 100% in the Annualized pRBCs Transfusion Volume

End point description:

Percentage of subjects with a reduction in the annualized mL/kg pRBCs transfused from 12 months post-drug product infusion through Month 24 (approximately a 12-month period) of at least 50%, 60%, 75%, 90% or 100% compared to the annualized mL/kg pRBC transfusion requirement during the 24 months prior to enrollment. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

12 months post-drug product infusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (not applicable)				
Reduction at >= 50%	95.7			
Reduction at >= 60%	91.3			
Reduction at >= 75%	91.3			
Reduction at >= 90%	91.3			
Reduction at 100%	91.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Volume of pRBC Transfusions

End point title	Annualized Volume of pRBC Transfusions

End point description:

Annualized volume of pRBC transfusions from 12 months post-drug product infusion through Month 24 was reported. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

From 12 months post-drug product infusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: milliliter/kilogram/year (mL/kg/year)				
arithmetic mean (standard deviation)	11.607 (± 40.2964)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Drug Product Infusion to Last pRBC Transfusion

End point title	Time from Drug Product Infusion to Last pRBC Transfusion

End point description:

Time from drug product infusion to last pRBC transfusion was reported. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

From start of drug product infusion up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: months				
median (full range (min-max))	0.953 (0.46 to 23.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Last pRBC Transfusion to the Month 24

End point title	Time From Last pRBC Transfusion to the Month 24

End point description:

Time From Last pRBC Transfusion to the Month 24 was reported. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

From last pRBC Transfusion up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: months				
median (full range (min-max))	23.228 (0.07 to 26.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weighted Average Nadir Hemoglobin (Hb)

End point title	Weighted Average Nadir Hemoglobin (Hb)

End point description:

The weighted average nadir Hb was defined as the most recent Hb prior to each pRBC transfusion, on the day of transfusion or within 3 days and, if there was a period of more than 60 days without transfusion, all Hb records between Day 61 and last follow-up or next transfusion (inclusive) was included. The weighted average nadir Hb during the period of 12 months post-drug product infusion to Month 24 was compared to the weighted average nadir Hb during the 24 months prior to enrollment. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

12 months post-drug product infusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: g/dL				
arithmetic mean (standard deviation)	9.546 (± 0.7007)			

Statistical analyses

No statistical analyses for this end point

Secondary: Unsupported Total Hb Levels at Month 6, 9, 12, 18 and 24

End point title	Unsupported Total Hb Levels at Month 6, 9, 12, 18 and 24

End point description:

Unsupported total Hb level was defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date. TP consisted of subjects who received LentiGlobin BB305 Drug Product infusion. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

At Month 6, 9, 12, 18 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: g/dL				
arithmetic mean (standard deviation)				
At Month 6 (n=22)	11.24 (± 1.249)			
At Month 9 (n=22)	11.22 (± 1.138)			
At Month 12 (n=21)	11.45 (± 1.314)			
At Month 18 (n=19)	11.80 (± 1.167)			
At Month 24 (n=20)	11.77 (± 1.224)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Unsupported Total Hb Levels (>=10 g/dL, >=11 g/dL, >=12 g/dL, >=13 g/dL, and >=14 g/dL) at Months 6, 9, 12, 18 and 24

End point title	Number of Subjects with Unsupported Total Hb Levels (>=10 g/dL, >=11 g/dL, >=12 g/dL, >=13 g/dL, and >=14 g/dL) at Months 6, 9, 12, 18 and 24

End point description:

The number of subjects with unsupported total Hb levels (>=10 g/dL, >=11 g/dL, >=12 g/dL, >=13 g/dL, and >=14 g/dL) meeting the thresholds were reported at at Months 6, 9, 12, 18 and 24. TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable at specific timepoint. Subjects were evaluable if they had an unsupported total Hb measurement at the specific timepoint, where unsupported total Hb level is defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.

End point type	Secondary

End point timeframe:

At Month 6, 9, 12, 18 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: subjects				
At Month 6 (>=10 g/dL) (n=22)	17			
At Month 6 (>=11 g/dL) (n=22)	15			
At Month 6 (>=12 g/dL) (n=22)	7			
At Month 6 (>=13 g/dL) (n=22)	1			
At Month 6 (>=14 g/dL) (n=22)	0			
At Month 9 (>=10 g/dL) (n=22)	20			
At Month 9 (>=11 g/dL) (n=22)	14			
At Month 9 (>=12 g/dL) (n=22)	5			
At Month 9 (>=13 g/dL) (n=22)	1			
At Month 9 (>=14 g/dL) (n=22)	0			
At Month 12 (>=10 g/dL) (n=21)	18			
At Month 12 (>=11 g/dL) (n=21)	14			
At Month 12 (>=12 g/dL) (n=21)	10			
At Month 12 (>=13 g/dL) (n=21)	1			
At Month 12 (>=14 g/dL) (n=21)	0			
At Month 18 (>=10 g/dL) (n=19)	18			
At Month 18 (>=11 g/dL) (n=19)	15			
At Month 18 (>=12 g/dL) (n=19)	8			
At Month 18 (>=13 g/dL) (n=19)	4			
At Month 18 (>=14 g/dL) (n=19)	0			
At Month 24 (>=10 g/dL) (n=20)	18			
At Month 24 (>=11 g/dL) (n=20)	14			
At Month 24 (>=12 g/dL) (n=20)	10			
At Month 24 (>=13 g/dL) (n=20)	5			
At Month 24 (>=14 g/dL) (n=20)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Have Not Received Chelation Therapy for At Least 6 Months Following Drug Product Infusion

End point title	Percentage of Subjects Who Have Not Received Chelation Therapy for At Least 6 Months Following Drug Product Infusion

End point description:

Percentage of subjects who have not received chelation therapy for at least 6 months following drug product infusion were reported. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (not applicable)	43.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Last Iron Chelation Use to Last Follow-up

End point title	Time from Last Iron Chelation Use to Last Follow-up

End point description:

Time from last iron chelation use to last follow-up to 24 months was reported. TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint. Subjects were evaluable for this endpoint if they had not received iron chelation therapy for at least 6 months following drug product infusion.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: months				
median (full range (min-max))	23.56 (17.6 to 24.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Used Therapeutic Phlebotomy Post DP infusion

End point title	Percentage of Subjects who Used Therapeutic Phlebotomy Post DP infusion

End point description:

Therapeutic phlebotomy could be used in lieu of chelation in subjects who had Hb consistently >= 11 g/dL and who were no longer receiving regular transfusions, at the discretion of the investigator.

Percentage of subjects who used therapeutic phlebotomy post DP infusion for up to Month 24 were reported. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (not applicable)	30.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in liver Iron Concentration by Magnetic Resonance Imaging (MRI)

End point title	Change From Baseline in liver Iron Concentration by Magnetic Resonance Imaging (MRI)

End point description:

Change From Baseline in liver Iron Content by Magnetic Resonance Imaging (MRI) at Months 12 and 24 were reported.TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint. Subjects were evaluable for this endpoint if they had available liver iron content measurements at baseline and at the applicable follow-up timepoints.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: milligrams per gram (mg/g)				
arithmetic mean (standard deviation)				
At Month 12	2.490 (± 4.1546)			
At Month 24	0.494 (± 3.9957)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cardiac T2* on MRI

End point title	Change From Baseline in Cardiac T2* on MRI

End point description:

Change From Baseline in Cardiac T2* on MRI at baseline, month 12 and 24 was reported. TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable at specific timepoint. Subjects were evaluable for this endpoint if they had available cardiac T2* measurements at baseline and at the applicable follow-up timepoints.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: milliseconds				
arithmetic mean (standard deviation)				
At Month 12 (n=19)	-1.0 (± 5.93)			
At Month 24 (n=21)	-1.6 (± 7.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Ferritin at Months 12 and 24

End point title	Change From Baseline in Serum Ferritin at Months 12 and 24

End point description:

Serum ferritin was commonly used for an indirect estimation of body iron stores. Although sensitive, it is not specific for iron overload as it can be elevated in a variety of infectious and inflammatory states, and in the presence of cytolysis. Change from baseline in serum ferritin at months 12 and 24 was reported. TP included all subjects who received beti-cel. Subjects were evaluable for this endpoint if they had available serum ferritin measurements at baseline and at the applicable follow-up timepoints.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: picomole per Liter (pmol/L)				
arithmetic mean (standard deviation)				
At Month 12 (n=22)	167.3 (± 1887.67)			
At Month 24 (n=23)	-1163.8 (± 2435.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Total Scores at Months 12 and 24

End point title	Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Total Scores at Months 12 and 24

End point description:

PedsQL GCS designed to measure health-related quality of life in pediatric and adolescents (2 to 18 years). It encompassed 4 dimensions of functioning (physical [8 items], emotional [5 items], social [5 items], school [3 items]). Age groups: Toddler (2-4 years), Young pediatric (5-7 years), Pediatric (8-12 years), Teens (13-18 years). Depending on subject's age, questionnaire was completed by parent/caregiver as appropriate. For Toddler group, consisted of 21 items, using a 5-point Likert scale (0 to 4); for all other groups, consisted of 23 items, with a 3-point Likert scale (0, 2, 4) for young pediatric, a 5-point Likert scale for pediatric and teens groups. All scores were transformed on a scale from 0 to 100 where 0=100, 1=75, 2=50, 3=25, and 4=0. Higher scores means improved quality of life. TP population. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: score on a scale				
arithmetic mean (standard deviation)				
Parent total score: Change at Month 12 (n=12)	8.76 (± 12.071)			
Parent total score: Change at Month 24 (n=14)	6.03 (± 9.753)			
Patient total score: Change at Month 12 (n=11)	6.82 (± 16.079)			
Patient total score: Change at Month 24 (n=12)	9.96 (± 16.997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y) VAS Health Status at Months 12 and 24

End point title	Change From Baseline in EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y) VAS Health Status at Months 12 and 24

End point description:

EQ-5D was validated, standardized, generic instrument that is most widely used preference based health related quality of life questionnaire in cost effectiveness and health technologies assessment. EQ-5D-Y was a version of instrument specifically developed and validated for use by youths aged 12 through 17 years. Components assess level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, anxiety and depression. Score scale for each domain scored on 3-level scale from 1 ("I have no problems/pain/anxiety/worry") to 3 ("I have a lot of problems/pain/anxiety/worry"). Respondents used EQ vertical, graduated Visual Analogue Scale (VAS) health status to rate their own health between 0 (worst) and 100 (best health state he/she can imagine). TP population. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Health State: Change at Month 12 (n=6)	15.8 (± 20.60)			
Health State: Change at Month 24 (n=7)	20.9 (± 18.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol-5D (EQ-5D) Heath Status Score

End point title	Change From Baseline in EuroQol-5D (EQ-5D) Heath Status Score

End point description:

EQ-5D was standardised measure of health status for combined EQ-5D-Y and EQ-5D-3L dimension. EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) which are

summed up. EQ-5D-3L and EQ-5D-Y descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Score scale for each domain scored on a 3-level scale from 1 (“I have no problems/pain/anxiety/worry”) to 3 (“I have a lot of problems/pain/anxiety/worry”). Health state of EQ-5D score was calculated based on responses to 5 dimensions, providing a single value on scale from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health), with higher scores indicates better health utility. The TP population. Here, “number of subjects analysed” signifies those subjects who were evaluable for this endpoint and “n” signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: score on a scale				
arithmetic mean (standard deviation)				
Health state: Change at Month 12 (n=15)	10.5 (± 15.92)			
Health state: Change at Month 24 (n=16)	14.6 (± 17.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) Total Score

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) Total Score

End point description:

FACT-BMT assessed bone marrow transplant related concerns. Total score was sum of sub-scale scores for 5 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and Bone Marrow Transplantation Subscale. Each item scored on a 5-point Likert scale based on subject agreement with each statement: 0 for "not at all," 1 for "a little bit," 2 for "somewhat," 3 for "quite a bit," and 4 for "very much. After taking into account reverse scores for questions constructed in negative form, subscale score for each domain was calculated by multiplying sum of item scores by number of items in subscale, then dividing by number of items answered. Total score was sum of subscale total added together and ranges from 0-148. Higher the score, better the quality of life. TP population. Here, “number of subjects analysed” signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: score on a scale				
arithmetic mean (standard deviation)				
Total Score: Change at Month 12 (n=9)	3.78 (± 16.994)			
Total Score: Change at Month 24 (n=9)	2.15 (± 13.695)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form-36 Health Survey (SF-36), Version 2, Acute (Physical and Mental Component Summary Scores) at Months 12 and 24

End point title	Change From Baseline in Short Form-36 Health Survey (SF-36), Version 2, Acute (Physical and Mental Component Summary Scores) at Months 12 and 24

End point description:

SF-36 was generic quality-of-life instrument, consisted of 36 items, were aggregated into 8 multi-item scales (physical functioning [1=yes, limited a lot to 3=no, not limited at all], role-physical [1=all of time to 5=none of time], bodily pain [1=very severe to 6=none], general health [1=poor to 5=excellent], vitality [1=none of time to 5=all of time], social functioning [1=all of time: to 5=none of time], role emotional [1=all of time to 5=none of time] and mental health [1=all of time to 5=none of the time]). Four domains comprised physical component summary (PCS) score (physical functioning, role-physical, bodily pain, general health) and remaining 4 domains comprised mental component summary (MCS) score (vitality, social functioning, role-emotional, mental health). TP population. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Component: Change at Month 12 (n=9)	0.80 (± 4.838)			
Physical Component: Change at Month 24 (n=9)	0.82 (± 3.672)			
Mental Component: Change at Month 12 (n=9)	1.88 (± 8.201)			
Mental Component: Change at Month 24 (n=9)	0.93 (± 10.805)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Phlebotomy Therapy Usage Following Drug Product Infusion

End point title	Annualized Phlebotomy Therapy Usage Following Drug Product Infusion

End point description:

Annualized phlebotomy therapy usage (number of procedures per year, calculated from DP infusion through last follow-up) were reported. TP included all subjects who received beti-cel. Here, "number of subjects analysed" signifies those subjects who received therapeutic phlebotomy.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: number of procedures per year				
arithmetic mean (standard deviation)	6.29 (± 4.786)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of pRBC Transfusions

End point title	Annualized Number of pRBC Transfusions

End point description:

Annualized number of pRBC transfusions from 12 months post-drug product infusion through Month 24 were reported. TP consisted of subjects who received LentiGlobin BB305 Drug Product infusion.

End point type	Secondary

End point timeframe:

From 12 months post-drug product infusion through Month 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: number of pRBC transfusions				
arithmetic mean (standard deviation)	0.95 (± 3.195)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From date of informed consent up to Month 24	
Adverse event reporting additional description:	
ITT population included all subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	LentiGlobin BB305 Drug Product
Reporting group description:	
Subjects <= 50 years of age received a single IV infusion of LentiGlobin BB305 Drug Product at a dose of >= 5.0 × 10^6 CD34+ cells/kg following myeloablative conditioning with busulfan (termed the Transplant population). As appropriate, data are analysed at times based on Intent-to-Treat (ITT) population which included all 24 subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.	

Serious adverse events	LentiGlobin BB305 Drug Product		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 24 (58.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion reaction			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Catheter site haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Appendicitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LentiGlobin BB305 Drug Product		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
General disorders and administration site conditions			
Catheter site pain			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Mucosal inflammation			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Non-cardiac chest pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	21		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	18		
Hypoxia			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Pharyngeal inflammation			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Rhinitis allergic			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Alanine aminotransferase increased			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	9		
Blood alkaline phosphatase increased			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Blood magnesium decreased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Blood bilirubin increased			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	16		
Skin abrasion			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Transfusion reaction			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 24 (70.83%)		
occurrences (all)	43		

Febrile neutropenia subjects affected / exposed occurrences (all)	8 / 24 (33.33%) 8		
Leukocytosis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Leukopenia subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 38		
Lymphopenia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
Neutropenia subjects affected / exposed occurrences (all)	18 / 24 (75.00%) 52		
Thrombocytopenia subjects affected / exposed occurrences (all)	24 / 24 (100.00%) 78		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 15		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Anal fissure subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Anal haemorrhage subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Anal inflammation			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	13		
Dyspepsia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Gingival bleeding			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	14 / 24 (58.33%)		
occurrences (all)	25		
Stomatitis			
subjects affected / exposed	18 / 24 (75.00%)		
occurrences (all)	35		
Vomiting			
subjects affected / exposed	16 / 24 (66.67%)		
occurrences (all)	36		
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	9		
Pigmentation disorder			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pruritus			

subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Skin hyperpigmentation			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Skin hypopigmentation			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Folliculitis			

subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Molluscum contagiosum			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	9		
Fluid overload			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	7		
Hypomagnesaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		

Hypophosphataemia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2016	Protocol Amendment Version 1.3: • Original protocol submitted to Health Authorities for regulatory approval.
05 January 2017	Protocol Amendment Version 2.0: • Included changes from country specific protocol Version 1.6 • Added study cohort of subjects <12 years of age and increased the number of subjects in the study as a result of this added cohort
19 June 2018	Protocol Amendment Version 3.0: • Updated secondary efficacy endpoints to include weighted average Hb during TI, transfusion volume from Month 12 through Month 24, and total Hb levels. All these data were already collected as part of the study and used to calculate other endpoints. • Corrected secondary efficacy endpoint of characterization of TR to be assessed for all subjects, not just for subjects who don't achieve TI • Corrected description of pharmacodynamic endpoint of βA-T87Q-globin expression • Removed requirement for repeating bone marrow aspiration as risks outweigh the benefits • Added requirement of prophylaxis with ursodeoxycholic acid (preferred) or defibrotide is required before initiation of conditioning to help prevent the occurrence of VOD/SOS. • Adjusted the target busulfan AUC, added recommendation for q6h dosing regimen for children and adolescents to avoid higher peak concentrations of busulfan, to reduce potential incidence of VOD/SOS • Clarified that SUSARs associated with the use of plerixafor will also be reported • Clarified planned interim analyses and primary endpoint failure definition • Updated baseline value for laboratory parameters to the most recent assessment prior to mobilization • Updated safety analysis of AEs time periods (e.g. collection modified in relation to each subject's time to NE rather than a specified day post drug product infusion)

05 April 2019	Protocol Amendment Version 4.0: • Included changes from country specific protocol Version 3.1 • Updated secondary efficacy endpoint to include time from drug product infusion to achievement of TI • Clarified that the volume and number of transfusions will be annualized for the period from 12 months post-drug product infusion, rather than from Month 12 through Month 24. • Moved parameter of 'time from last pRBC transfusion to Month 24' under characterization of TR to be assessed for all subjects, and not just for subjects achieving TI • Updated secondary efficacy endpoint to calculate weighted average nadir Hb to more accurately capture Hb levels over time. • Updated secondary efficacy endpoint to analyze unsupported total Hb compared to total Hb to reduce the contribution of transfused pRBCs to total Hb assessments. • Updated parameters for the secondary efficacy endpoints of characterization of use of iron chelation therapies, including adding the use of phlebotomy to more accurately capture iron removal strategies. • Re-categorized quality of life (QoL) parameters as secondary endpoints instead of exploratory efficacy endpoints. • Updated efficacy endpoint of 'correlations of pre-treatment variables with response' to remove β/α globin ratio as an example of pre-treatment variables and to add peripheral blood, VCN, and HbAT87Q as examples of response parameters. • Updated endpoint on measures of health resource utilization to clarify it is measuring annualized number of transfusions and annualized corresponding parameters, to remove iron chelation usage assessment, and to measure number of days hospitalized from Month 12 through Month 24. • Added efficacy endpoint of length of in-patient stay from initiation of conditioning to discharge. • Added additional safety endpoint to characterize the incidence of acute and chronic graft-versus-host disease (GVHD) to ensure that any occurrence of GVHD is adequately assessed in this study.
06 October 2020	Protocol Amendment Version 5.0: • Updated the assessment of clonal predominance to be based on frequency of clones with LVV insertions rather than on frequency of individual LVV insertion sites. • Separated the safety endpoint for insertional oncogenesis and clonal predominance into two endpoints, with insertional oncogenesis as a secondary endpoint and clonal predominance as an exploratory endpoint. Designated the remaining safety endpoints as secondary endpoints. • Added text to provide guidelines around study procedures impacted by force of nature events and analysis of assessments impacted by the COVID-19 pandemic. • Added text to indicate that clinical work-up for unexpected blood test results may be performed. • Clarified that SAEs that start between completion of the parent study and enrollment in long-term follow-up Study LTF-303 will be recorded in the HGB-207 SAE report form. • Following regulatory correspondence, added text to extend the time period for follow-up of newborns
10 June 2021	.Protocol Amendment Version 6.0: • Updated clinical work-up criteria, procedure and follow-up describing Integration Site Analysis. • Optional archival and genetic testing on Bone Marrow samples. Updated schedule of events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported