Clinical trial results:
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent -Thalassemia, 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	2016-003611-35
Trial protocol	GB DE GR FR IT
Global end of trial date	15 November 2022

Results information

Result version number	v1 (current)
This version publication date	28 May 2023
First version publication date	28 May 2023

Trial information

Trial identification

Sponsor protocol code	HGB-212

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03207009
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	bluebird bio, Inc.
Sponsor organisation address	455 Grand Union Blvd, Somerville, MA , United States, 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-000166-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	26 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2022
Global end of trial reached?	Yes
Global end of trial date	15 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the efficacy of treatment with LentiGlobin BB305 Drug Product (beti-cel) in subjects less than or equal to (<=) 50 years of age with transfusion-dependent beta-thalassemia (TDT), who have a beta0/beta0, beta0/IVS-I-110, or IVS-I-110/IVS-I-110 genotype at the 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 June 2017
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	United Kingdom: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	19
EEA total number of subjects	8

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)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study centers in France, Germany, Greece, Italy, United Kingdom, and United States, of which 8 had enrolled subjects from 08 June 2017 to 15 November 2022.

Pre-assignment

Screening details:

A total of 19 subjects were enrolled, of which 18 subjects aged <=50 years were treated with 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) body weight on Day 1 after myeloablative conditioning with busulfan (4 days of conditioning followed by at least 48 hours of washout) (termed the Transplant population).

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 body weight of LentiGlobin BB305 Drug Product.

Number of subjects in period 1	LentiGlobin BB305 Drug Product
Started	19
Completed	18
Not completed	1
Withdrew consent prior to conditioning	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

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) body weight on Day 1 after myeloablative conditioning with busulfan (4 days of conditioning followed by at least 48 hours of washout) (termed the Transplant population). As appropriate, data are analysed at times based on Intent-to-Treat (ITT) population which included all 19 subjects who initiated any study procedures, beginning with mobilization by G-CSF and/or plerixafor.

Reporting group values	Overall Study	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 12.0 4.0 to 33.0	 -	
Gender categorical Units: Subjects			
Female	9	9	
Male	10	10	
Race Units: Subjects			
Asian	8	8	
White	10	10	
Not Provided	1	1	
Ethnicity Units: Subjects			
Not Hispanic or Latino	18	18	
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) body weight on Day 1 after myeloablative conditioning with busulfan (4 days of conditioning followed by at least 48 hours of washout) (termed the Transplant population).

Primary: Percentage of Subjects who have Achieved Transfusion Independence (TI)

End point title	Percentage of Subjects who have Achieved 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, have not achieved TI in their parent study, or completed their parent study.

End point type	Primary

End point timeframe:

From 12 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	18			
Units: percentage of subjects				
number (confidence interval 95%)	88.9 (65.3 to 98.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who have Achieved Transfusion Independence (TI) at Month 24

End point title	Percentage of Subjects who have Achieved 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. TP included all subjects who received beti-cel. Subjects evaluable for TI are defined as subjects who have achieved TI, have not achieved TI in their parent study, or completed their parent study. Here, "number of subjects analysed" signifies those subjects who achieved TI.

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	18			
Units: percentage of subjects				
number (confidence interval 95%)	88.9 (65.3 to 98.6)			

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. TP included all subjects who received beti-cel. Subjects evaluable for TI are defined as subjects who have achieved TI, have not achieved TI in their parent study, or completed their parent study. Here, "number of subjects analysed" signifies those subjects who achieved TI. Data are presented through the Month 24 Visit based on calendar dates and including visit windows.

End point type	Secondary

End point timeframe:

From start of TI up to Month 24 (actual maximum time frame of up to approximately 25 months due to visit window)

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: months				
median (full range (min-max))	20.86 (13.1 to 25.4)			

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. Subjects evaluable for TI are defined as subjects who have achieved TI, have not achieved TI in their parent study, or completed their parent study. Here, "number of subjects analysed" signifies those subjects who achieved TI. Data are presented through the Month 24 Visit based on calendar dates and including visit windows.

End point type	Secondary

End point timeframe:

From 14 months post-drug product infusion through Month 24 (actual maximum time frame of up to approximately 25 months due to visit window)

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: months				
median (full range (min-max))	15.67 (14.8 to 24.5)			

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 average Hb was defined as the weighted average of Hb values without any pRBC transfusions in the proceeding 60 days. Ratio of the time between two Hb values and the time between the first and the last Hb values was used as the weight for calculation. TP included all subjects who received beti-cel. Subjects evaluable for TI are defined as subjects who have achieved TI, have not achieved TI in their parent study, or completed their parent study. 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	16			
Units: g/dL				
arithmetic mean (standard deviation)	10.817 (± 1.2535)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who meet the Definition of Transfusion Reduction (TR)

End point title	Percentage of Subjects who meet the Definition of Transfusion Reduction (TR)

End point description:

TR was defined as demonstration of a 60 percent (%) reduction in the annualized volume of pRBC transfusion requirements (in milliliter per kilogram [mL/kg]) in the post-treatment time period from 12 Months post-drug product infusion through Month 24 compared to the annualized mL/kg pRBC transfusion requirement during the 24 months prior to study enrollment. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From 12 to 24 months post-transplant

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of subjects				
number (confidence interval 95%)	94.4 (72.7 to 99.9)			

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	18			
Units: percentage of subjects				
number (confidence interval 95%)				
Reduction at >= 50%	94.4 (72.7 to 99.9)			
Reduction at >= 60%	94.4 (72.7 to 99.9)			
Reduction at >= 75%	94.4 (72.7 to 99.9)			
Reduction at >= 90%	94.4 (72.7 to 99.9)			
Reduction at 100%	88.9 (65.3 to 98.6)			

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 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	18			
Units: pRBC transfusions per year				
arithmetic mean (standard deviation)	0.68 (± 2.701)			

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 compared to the annualized volume of transfusions during the 24 months prior to enrollment. TP included all subjects who received beti-cel.

End point type	Secondary

End point timeframe:

From 12 to 24 months post-transplant

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: milliliter/kilogram/year (mL/kg/year)				
arithmetic mean (standard deviation)	11.589 (± 47.4080)			

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	18			
Units: months				
median (full range (min-max))	0.986 (0.00 to 23.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Last pRBC Transfusion to 24 Months

End point title	Time From Last pRBC Transfusion to 24 Months

End point description:

Time From Last pRBC Transfusion to the Month 24 was reported. TP included all subjects who received beti-cel. Data are presented through the Month 24 Visit based on calendar dates and including visit windows.

End point type	Secondary

End point timeframe:

From last pRBC Transfusion up to Month 24 (actual maximum time frame of up to approximately 27 months due to visit window)

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (full range (min-max))	23.211 (0.16 to 27.47)			

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	18			
Units: g/dL				
arithmetic mean (standard deviation)	10.653 (± 1.5096)			

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	17			
Units: g/dL				
arithmetic mean (standard deviation)				
At Month 6 (n=17)	10.41 (± 1.253)			
At Month 9 (n=17)	10.61 (± 1.338)			
At Month 12 (n=17)	10.65 (± 1.619)			
At Month 18 (n=15)	11.00 (± 1.483)			
At Month 24 (n=17)	10.82 (± 1.580)			

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:

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 Months 6, 9, 12, 18 and 24. TP included all subjects who received beti-cel. 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. 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 Months 6, 9, 12, 18 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Subjects				
At Month 6 (>=10 g/dL) (n=17)	11			
At Month 6 (>=11 g/dL) (n=17)	4			
At Month 6 (>=12 g/dL) (n=17)	3			
At Month 6 (>=13 g/dL) (n=17)	1			
At Month 6 (>=14 g/dL) (n=17)	0			
At Month 9 (>=10 g/dL) (n=17)	13			
At Month 9 (>=11 g/dL) (n=17)	5			
At Month 9 (>=12 g/dL) (n=17)	3			
At Month 9 (>=13 g/dL) (n=17)	1			
At Month 9 (>=14 g/dL) (n=17)	0			
At Month 12 (>=10 g/dL) (n=17)	12			
At Month 12 (>=11 g/dL) (n=17)	6			
At Month 12 (>=12 g/dL) (n=17)	3			
At Month 12 (>=13 g/dL) (n=17)	2			
At Month 12 (>=14 g/dL) (n=17)	1			
At Month 18 (>=10 g/dL) (n=15)	13			
At Month 18 (>=11 g/dL) (n=15)	5			
At Month 18 (>=12 g/dL) (n=15)	3			
At Month 18 (>=13 g/dL) (n=15)	3			
At Month 18 (>=14 g/dL) (n=15)	0			
At Month 24 (>=10 g/dL) (n=17)	10			
At Month 24 (>=11 g/dL) (n=17)	7			
At Month 24 (>=12 g/dL) (n=17)	3			
At Month 24 (>=13 g/dL) (n=17)	3			
At Month 24 (>=14 g/dL) (n=17)	1			

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:

From 6 to 24 months

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of subjects				
number (not applicable)	61.1			

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. Subjects were evaluable for this endpoint if they had not received iron chelation therapy for at least 6 months following drug product infusion. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint. Data are presented through the Month 24 Visit based on calendar dates and including visit windows.

End point type	Secondary

End point timeframe:

From last Iron Chelation up to Month 24 (actual maximum time frame of up to approximately 29 months due to visit window)

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: months				
median (full range (min-max))	17.81 (0.3 to 28.9)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number 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. Number 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	18			
Units: Subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Liver Iron Content by Magnetic Resonance Imaging (MRI)

End point title	Change From Baseline in Liver Iron Content by Magnetic Resonance Imaging (MRI)

End point description:

Change From Baseline in Liver Iron Content by MRI at Months 12 and 24 were reported.TP included all subjects who received beti-cel. Subjects were evaluable for TI if they had completed the study (i.e., completed the Month 24 Visit), achieved TI, or did not achieve TI during the study. Baseline is defined as value closest to but prior to conditioning. Here, "n" signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: milligram per gram (mg/g)				
arithmetic mean (standard deviation)				
Change at Month 12 (n=17)	3.171 (± 5.4134)			
Change at Month 24 (n=18)	1.033 (± 4.4407)			

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 from baseline, month 12 and 24 was reported. TP included all subjects who received beti-cel. Subjects were evaluable for TI if they had completed the study (i.e., completed the Month 24 Visit), achieved TI, or did not achieve TI during the study. Here, "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	18			
Units: millisecond (ms)				
median (full range (min-max))				
Change at Month 12 (n=17)	-0.2 (-27 to 7)			
Change at Month 24 (n=18)	0.2 (-33 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Ferritin

End point title	Change From Baseline in Serum Ferritin

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. Subjects are evaluable for TI if they had completed the study (i.e., completed the Month 24 Visit), achieved TI, or did not achieve TI during the study. Here, "n" signifies those subjects who were evaluable at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: picomole per Liter (pmol/L)				
arithmetic mean (standard deviation)				
Change at Month 12 (n=17)	87.3 (± 1302.76)			
Change at Month 24 (n=18)	-605.2 (± 1716.90)			

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 (2-18 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). The questionnaire was also completed by parent/caregiver to assess parents' perceptions of their children's quality of life. The Toddler group consisted of 21 items, using a 5-point Likert scale (0 to 4); 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 reported scores were transformed on a scale from 0 to 100 for each domain where 0=100, 1=75, 2=50, 3=25, and 4=0. Higher scores correspond with higher quality of life. TP population. "Number of subjects analysed"=subjects who were evaluable for this endpoint; "n"=subjects were at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and 24

End point values	LentiGlobin BB305 Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: score of scale				
arithmetic mean (standard deviation)				
Parent total score: Change at Month 12 (n=13)	-6.20 (± 12.948)			
Parent total score: Change at Month 24 (n=12)	-3.49 (± 19.621)			
Patient total score: Change at Month 12 (n=11)	2.96 (± 14.857)			
Patient total score: Change at Month 24 (n=11)	4.84 (± 11.321)			

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 is a validated, standardized, generic instrument that was 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. The EQ-5D-Y visual analog scale (VAS) consisted of a 20-cm vertical VAS, with anchors of 0 ("worst imaginable health state") and 100 ("best imaginable health state"). Respondents were asked to rate their own health state today by drawing a line from a box containing these words to the point on the scale that they felt most accurately reflected their current health state. The VAS was reported (raw data) on a scale of 0-100 where 0= death and 100= perfect health. Higher scores equated to better outcomes. 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	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Month 12 (n=7)	0.3 (± 11.91)			
Change at Month 24 (n=7)	2.0 (± 12.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol Quality of Life 5-Dimension Adult Scale (EQ-5D-3L) VAS Heath Status Score at Months 12 and 24

End point title	Change From Baseline in EuroQol Quality of Life 5-Dimension Adult Scale (EQ-5D-3L) VAS Heath Status Score at Months 12 and 24

End point description:

EQ-5D is a validated, standardized, generic instrument that was most widely used preference based health related quality of life (HRQoL) questionnaire in cost effectiveness and health technologies assessment. Participants age >=18 at time of informed consent were eligible to complete the EQ-5D-3L which is a visual analog scale (VAS) which consists of a 20-cm vertical VAS, with anchors of 0 ("worst imaginable health state") and 100 ("best imaginable health state"). Respondents were asked to rate their own health state today by drawing a line from a box containing these words to the point on the scale that they feel most accurately reflects their current health state. TP population. Number of subjects analysed signifies 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	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Month 12	-3.6 (± 13.13)			
Change at Month 24	-2.4 (± 10.50)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

FACT-BMT is assessed bone marrow transplant related quality of life in adults. It. 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 participant 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. Reported scores were transformed as follows: 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 scores corresponded with higher quality of life. TP population. 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	4			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Month 12 (n=4)	0.33 (± 6.716)			
Change at Month 24 (n=4)	2.58 (± 4.246)			

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 designed to measure health-related quality of life in adults. The instrument consisted of 36 items, were aggregated into 8 multi-item scales (physical functioning [1=yes, limited a lot-3=no, not limited at all], role-physical [1=all of time-5=none of time], bodily pain [1=very severe to 6=none], general health [1=poor-5=excellent], vitality [1=none of time-5=all of time], social functioning [1=all of time-5=none of time], role emotional [1=all of time-5=none of time] and mental health [1=all of time-5=none of the time]). 4 domains comprised PCS score (physical functioning, role-physical, bodily pain, general health) and remaining 4 domains comprised MCS score (vitality, social functioning, role-emotional, mental health). Reported summary scores were transformed on a scale from 0-100. Higher scores corresponded with higher quality of life. TP population. 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	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Component: Change at Month 12 (n=5)	-0.89 (± 10.289)			
Physical Component: Change at Month 24 (n=5)	1.09 (± 8.167)			
Mental Component: Change at Month 12 (n=5)	2.42 (± 7.637)			
Mental Component: Change at Month 24 (n=5)	2.08 (± 7.281)			

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	2			
Units: Number of procedures per year				
arithmetic mean (standard deviation)	4.22 (± 3.192)			

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/kilogram (kg) body weight on Day 1 after myeloablative conditioning with busulfan (4 days of conditioning followed by at least 48 hours of washout) (termed the Transplant population).

Serious adverse events	LentiGlobin BB305 Drug Product		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Bartholin’s cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 19 (5.26%)		
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	19 / 19 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Focal nodular hyperplasia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Application site pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Application site swelling			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Catheter site pain			

subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Feeling cold			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	9		
Non-cardiac chest pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	6		
Puncture site pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	12		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	13		
Hypoxia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Laryngeal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pharyngeal inflammation			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Pulmonary mass			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Insomnia			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	11		
Blood bilirubin increased			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood testosterone decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Coombs direct test positive			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Pulmonary function test decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Weight decreased			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Incision site pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Post procedural discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	18		
Skin abrasion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Transfusion reaction			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	20		
Paraesthesia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 19 (78.95%)		
occurrences (all)	35		
Febrile neutropenia			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	11		
Immune thrombocytopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	15		
Lymphopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	16 / 19 (84.21%)		
occurrences (all)	37		
Neutrophilia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pancytopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	17 / 19 (89.47%)		
occurrences (all)	51		

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Chalazion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Conjunctival haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Anal inflammation			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Gingival bleeding			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lip dry			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	13		
Oral pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Palatal ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	12 / 19 (63.16%)		
occurrences (all)	19		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hepatic mass			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	12 / 19 (63.16%)			
occurrences (all)	13			
Dermatitis contact				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	4			
Ecchymosis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
Hidradenitis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Intertrigo				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Petechiae				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
Rash				
subjects affected / exposed	4 / 19 (21.05%)			
occurrences (all)	5			
Rash macular				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Skin exfoliation				

subjects affected / exposed occurrences (all) Skin hyperpigmentation subjects affected / exposed occurrences (all) Skin hypopigmentation subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 5 / 19 (26.32%) 5 1 / 19 (5.26%) 1 1 / 19 (5.26%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Endocrine disorders Delayed puberty subjects affected / exposed occurrences (all) Hypogonadism subjects affected / exposed occurrences (all) Secondary hypogonadism subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	7		
Flank pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Osteopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Cystitis			

subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Lice infestation				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Mucosal infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	4 / 19 (21.05%)			
occurrences (all)	6			
Oral herpes				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	4			
Pyelonephritis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Rhinovirus infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Staphylococcal infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Systemic infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Upper respiratory tract infection				

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Varicella zoster virus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	7		
Hyperchloraemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	9		
Hypokalaemia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		

Metabolic acidosis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Vitamin K deficiency subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2018	Amendment version 2.0: Part 1: • Target average daily busulfan AUC reduced from 4500 (range 4000 to 5000) mcM*min to 4200 (range 3800 to 4500) mcM*min. Children and adolescents were recommended to follow a q6h dosing regimen, with a target AUC of 1050 (range 950 to 1125) mcM*min. Prophylaxis with ursodeoxycholic acid (preferred) or defibrotide is required before initiation of conditioning to help prevent the occurrence of VOD/SOS. •Modified select secondary efficacy endpoints: Added secondary efficacy endpoints for weighted average Hb during TI, time from drug product infusion to achievement of TI, and number of days hospitalized; data were already collected as part of the study. Rephrased the parameters used to assess transfusion-free periods, added under characterization of TR to be assessed for all subjects. Added secondary efficacy endpoints for total Hb over time and at specific levels to provide additional analysis of hematological parameters. Updated secondary efficacy endpoints for weighted average nadir Hb and volume of pRBC transfusions from Month 12 through Month 24; transfusion volume data had already been collected and used to calculate the primary endpoint. Added secondary efficacy endpoint for the use of phlebotomy and removed parameter for iron chelation usage as it is unlikely to be meaningful due to the large variation in iron chelation agents and routes of administration which do not allow for a clear comparison. • Added safety endpoint to characterize the incidence of graft-vs-host disease (GVHD) to ensure that any occurrence of GVHD is adequately assessed amongst the AEs that are currently collected as part of this study. • Added minimum enrollment for subjects without an IVS-I-110 mutation to ensure heterogenous representation of β0/β0 subjects reflective of the general genotypic distribution.
19 June 2018	Amendment version 2.0: Part 2: • Modified the time period for AE collection to be in relation to each subject's time of neutrophil engraftment rather than to a specified Day post drug product infusion because subjects have differing amounts of time until neutrophil engraftment. Added time period "from informed consent/assent through Month 24 Visit" to ensure adequate assessment of AEs during the study.

05 April 2019	Amendment version 3.0: • Included changes from country-specific protocol Version 2.1. • Clarified that transfusion requirements, use of iron removal therapies, and weighted average nadir Hb measurements will be annualized so that they can be fairly compared across time periods. • Modified select secondary efficacy endpoints: Adjusted secondary endpoints for total Hb levels to unsupported total Hb levels to reduce the contribution of transfused pRBCs to total Hb assessments. Added new secondary endpoint of "Time from last iron chelation use to last follow-up", allowing assessment of iron chelation use independent of dose information. Re-categorized quality of life (QoL) parameters as secondary endpoints instead of exploratory efficacy endpoints, as QoL are clinically meaningful parameters for assessing additional effects of treatment. Separated the "Length of in-patient hospital stay from initiation of conditioning to discharge" endpoint from the other health resource utilization endpoints and added it as an individual endpoint. This parameter was not intended for comparison with the pre-enrollment period. • Prohibited the use of hydroxyurea during the study, and included luspatercept (a potential new drug on the market) as an additional example of a potentially disease-modifying therapy. • Added recommendation to not use anti-retroviral medicines before mobilization and after drug product infusion, as they could theoretically interfere with the efficacy of the drug product. • Corrected the SOE to add assessment of immunological parameters at end-of-study visit Month 24. • Integration site analyses were updated to include qPCR to improve precision.
16 August 2019	Amendment version 4.0: • Sample size number has been increased from approximately 15 to approximately 18 subjects (with at least 2 additional subjects with a β0/β0 genotype) to reflect the number of subjects that have or are intended to be treated. • To account for the increase in sample size, the 70% success criterion has been updated from 11 out of 15 subjects to 13 out of 18 subjects, and the lower 1-sided confidence bound has been updated from 44.9% to 46.5%.
18 October 2020	Amendment version 5.0: • Replaced the former primary endpoint of TR with TI. TI is a more meaningful clinical outcome than TR, and is to be used for regulatory decision making as discussed with regulatory authories. • Moved TR into the secondary endpoints. • To account for the new primary endpoint of TI, the success criterion, sample size estimation, and statistical analyses for the primary and secondary endpoints were updated. • Updated the assessment of clonal predominance, which will now be assessed based on the frequency of clones with lentiviral vector (LVV) insertions rather than the frequency of individual LVV integration site (IS). Clonal contribution as determined by IS-specific qPCR normalized against human genomic genes is the most suitable current method available to accurately determine the relative predominance of each given clone independent of how many unique IS may be present within that clone. • Designated clonal predominance as an exploratory safety endpoint and the remaining safety endpoints as secondary endpoints. • Added text to provide guidelines around study procedures impacted by the force of nature events and analysis of assessments impacted by the COVID-19 pandemic. • Updated clinical laboratory tests to allow for further investigator when additional follow-up may be required (e.g., unexpected blood test results). • 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-212 SAE report form. • Added text to extend the time period for follow-up of newborns after regulatory correspondence.

10 June 2021	Amendment version 6.0: • Updated the criteria for which a clinical work-up following ISA is recommended, updated the clinical work-up procedure to include a follow-up ISA, and updated the process to be used upon detection of clonal predominance or malignancy. These updates allowed for more stringent monitoring for malignancies or potential malignancies following treatment with beti-cel. • Specified that bone marrow samples may be archived and that genetic testing may be performed if clinically indicated. • Provided considerations for vaccines as concomitant medications per guidance from regulatory agency. • Removed the statement that a subject may be withdrawn from the study if they have undetectable VCN in peripheral blood cells for 2 consecutive measurements at least 1 month apart.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported