



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | HGB-205 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001665-PIP02-17 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

PIP was available only for SCD subjects.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 3 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | LentiGlobin BB305 Drug Product for SCD |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--|
| Arm title | LentiGlobin BB305 Drug Product for TDT |
|------------------|--|

Arm description:

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

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

Dosage and administration details:

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

| Number of subjects in period 1 | LentiGlobin BB305 Drug Product for SCD | LentiGlobin BB305 Drug Product for TDT |
|---------------------------------------|--|--|
| Started | 3 | 4 |
| Completed | 3 | 4 |

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | LentiGlobin BB305 Drug Product for SCD |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | LentiGlobin BB305 Drug Product for TDT |
|-----------------------|--|

Reporting group description:

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

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

| | |
|-----------------|---|
| End point title | Number of Treated Subjects With Successful Neutrophil and Platelet Engraftment ^[1] |
|-----------------|---|

End point description:

Neutrophil engraftment was defined as the first of absolute neutrophil count (ANC) $>$ or $= 0.5 \times 10^9$ /liter (L) for 3 consecutive days (or 3 consecutive measurements done on separate days), after a post-transplant value less than [$<$] 0.5×10^9 /L). Platelet engraftment was defined as the first of 3 consecutive platelet values $>$ or $= 20 \times 10^9$ /L for subjects with TDT and values $>$ or $= 50 \times 10^9$ /L for subjects with SCD obtained on different days with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. The day of engraftment is the first day of the 3 consecutive platelet measurements. This endpoint was evaluated in the Transplant Population (TP), which included all subjects in the intent-to-treat (ITT) population who underwent LentiGlobin BB305 Drug Product infusion.

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Time to Successful Neutrophil and Platelet Engraftment

| | |
|-----------------|---|
| End point title | Time to Successful Neutrophil and Platelet Engraftment ^[2] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Transplant Related Mortality

| | |
|-----------------|--|
| End point title | Incidence of Transplant Related Mortality ^[3] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From screening through 365 days post-transplant

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival

| | |
|-----------------|---------------------------------|
| End point title | Overall Survival ^[4] |
|-----------------|---------------------------------|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Vector-Derived Replication-Competent Lentivirus (RCL) ^[5] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of Treated Subjects With (>) 30 Percent (%) Contribution of an Individual Clone As Per Integration Site Analysis (ISA) ^[6] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events (AEs) and Serious |
|-----------------|--|

End point description:

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

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

End point timeframe:

From date of Informed Consent up to Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Percentage of Treated TDT Subjects Who Achieved Transfusion independence (TI) ^[8] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Weighted Average Hemoglobin (Hb) During Period of Transfusion Independence (TI) ^[9] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Transfusion Independence (TI)

| | |
|-----------------|---|
| End point title | Duration of Transfusion Independence (TI) ^[10] |
|-----------------|---|

End point description:

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

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Time From LentiGlobin BB305 Drug Product Infusion to Last Packed Red Blood Cells (pRBC) Transfusion Prior to Achieving Transfusion Independence (TI) ^[11] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Time from LentiGlobin BB305 Drug Product Infusion to Achieving Transfusion Independence (TI) ^[12] |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Weighted Average Nadir Hemoglobin (Hb)

| | |
|-----------------|--|
| End point title | Weighted Average Nadir Hemoglobin (Hb) ^[13] |
|-----------------|--|

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

Notes:

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Therapeutic Globin Expression Measured by Hb Containing β^A -T87Q Globin (HbA^{T87Q}) in Peripheral Blood

| | |
|-----------------|---|
| End point title | Therapeutic Globin Expression Measured by Hb Containing β^A -T87Q Globin (HbA ^{T87Q}) in Peripheral Blood |
|-----------------|---|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

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

Statistical analyses

No statistical analyses for this end point

Secondary: Vector Copy Number (VCN) in Peripheral Blood

| | |
|-----------------|--|
| End point title | Vector Copy Number (VCN) in Peripheral Blood |
|-----------------|--|

End point description:

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

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

End point timeframe:

From time of drug product infusion through Month 24 visit

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of informed consent through Month 24 visit

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | LentiGlobin BB305 Drug Product for SCD |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | LentiGlobin BB305 Drug Product for TDT |
|-----------------------|--|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

PIP was available only for SCD subjects.

Notes: