# STATISTICAL ANALYSIS PLAN

## A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia, who do not have a $\beta^0/\beta^0$ Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector in Subjects ≤50 Years of Age

## Protocol HGB-207

| | |
|---|---|
| **Protocol Number:** | HGB-207 |
| **Protocol Version and Date:** | Version 6.0: 10 June 2021 |
| **Name of Test Drug:** | betibeglogene autotemcel (also known as LentiGlobin BB305 Drug Product for the treatment of β-thalassemia) |
| **Phase:** | Phase 3 |
| **Methodology:** | Open-label, Safety, and Efficacy |
| **Sponsor:** | bluebird bio, Inc.<br>60 Binney Street<br>Cambridge, MA 02142 USA |
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| **Analysis Plan Date:** | 13 January 2022 |
| **Analysis Plan Version:** | Version 5.0 |

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# APPROVAL OF STATISTICAL ANALYSIS PLAN
# SIGNATURE PAGE

**Title: A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia, who do not have a $\beta^0/\beta^0$ Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector in Subjects ≤50 Years of Age**

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**Approval:**
By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ANC | Absolute neutrophil count |
| AUC | Area under the curve |
| BMTS | Bone marrow transplantation subscale |
| CBC | Complete blood count |
| CI | Confidence interval |
| CRF | Case report form |
| CS | Clinically significant |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLco | Diffusing capacity for carbon monoxide |
| DMC | Data Monitoring Committee |
| EPO | Erythropoietin |
| EQ-5D | EuroQoL-5D |
| EQ-5D-Y | EuroQol-5D-Youth version |
| FACT-BMT | Functional Assessment of Cancer Therapy - Bone Marrow Transplantation |
| FACT-G | Functional Assessment of Cancer Therapy - General |
| G-CSF | Granulocyte colony-stimulating factor |
| GRRs | Global reference ranges |
| Hb | Hemoglobin |
| HbA | Hemoglobin A |
| *HBB* | β-globin gene |
| HbE | Hemoglobin E |
| HbF | Hemoglobin F |
| HIV | Human immunodeficiency virus |
| HPLC | High-performance liquid chromatography |
| HRQoL | Health-related quality of life |
| HSC | Hematopoietic stem cell |
| HSCT | Hematopoietic stem cell transplant(ation) |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IRT | Item response theory |
| IS | Integration site |
| ISA | Integration site analysis |
| ITT | Intent-to-treat |
| IV | Intravenous |
| KM | Kaplan-Meier |
| LDH | Lactate dehydrogenase |
| LIC | Liver iron content |
| LVEF | Left ventricular ejection fraction |
| MCH | Mean corpuscular hemoglobin |
| MCS | Mental component summary |

| Abbreviation | Definition |
|---|---|
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| OS | Overall survival |
| PBL | Peripheral blood leukocyte |
| PBMC | Peripheral blood mononuclear cell |
| PCS | Physical component summary |
| PedsQL | Pediatric Quality of Life Inventory |
| pRBC | Packed red blood cell(s) |
| QoL | Quality of life |
| RBC | Red blood cell(s) |
| RCL | Replication competent lentivirus |
| Rel Day | Relative study day |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SEP | Successful engraftment population |
| SF-36 | Short Form-36 |
| SI | International system of units |
| SOC | System organ class |
| SOE | Schedule of events |
| TDT | Transfusion-dependent β-thalassemia |
| TI | Transfusion independence |
| TP | Transplant population |
| TR | Transfusion reduction |
| VCN | Vector copy number |
| WBC | White blood cell |
| WHO | World Health Organization |

# 1. INFORMATION FROM THE STUDY PROTOCOL

## 1.1. Introduction and Objectives

### 1.1.1. Introduction

This document is the statistical analysis plan (SAP) for Study HGB-207, "A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia (TDT), who do not have a $\beta^0/\beta^0$ Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector in Subjects ≤50 Years of Age." It is based on Protocol Version 6.0, dated 10 June 2021.

The SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this study.

### 1.1.2. Study Objectives

**Primary objective:**

- Evaluate the efficacy of treatment with LentiGlobin BB305 Drug Product in subjects ≤50 years of age with TDT who do not have a $\beta^0/\beta^0$ genotype at the β-globin *(HBB)* gene

**Secondary objective:**

- Evaluate the safety of treatment with LentiGlobin BB305 Drug Product in subjects ≤50 years of age with TDT who do not have a $\beta^0/\beta^0$ genotype at the *HBB* gene

## 1.2. Study Design

### 1.2.1. Synopsis of Study Design

This is a single-arm, open-label, multi-site, single-dose, Phase 3 study with 2 cohorts of subjects with TDT who do not have a $\beta^0$ mutation at both alleles of the *HBB* gene (i.e., non-$\beta^0/\beta^0$): Cohort 1 includes at least 15 subjects ≥12 and ≤50 years of age, and Cohort 2 includes at least 8 subjects <12 years of age who must have a history of transfusion of at least 100 mL/kg/year of packed red blood cells (pRBCs) in the 2 years preceding enrollment and weigh a minimum of 6 kg and reasonably be anticipated to be able to provide at least the minimum number of cells required to initiate the manufacturing process. TDT is defined by a history of at least 100 mL/kg/year of pRBCs or being managed under standard thalassemia guidelines (e.g. Thalassemia International Federation, 2014) with ≥8 transfusions of pRBCs per year in the 2 years preceding enrollment.

Patients transplanted at younger ages before advanced disease symptoms of thalassemia are manifested are hypothesized to have different rates of transplant-related complications, different long-term disease outcomes, and potentially different efficacy of gene transduction than adult patients. The study will evaluate the safety and efficacy of autologous hematopoietic stem cell

transplantation (HSCT) using LentiGlobin BB305 Drug Product (autologous CD34+ cell-enriched population that contains hematopoietic stem cells transduced with BB305 lentiviral vector encoding the $\beta^{A\text{-}T87Q}$-globin, suspended in cryopreservation solution).

Treatment will proceed in a staggered fashion. After 2 subjects ≥12 years of age have attained neutrophil engraftment (NE) after LentiGlobin BB305 Drug Product infusion in Cohort 1, the independent Data Monitoring Committee (DMC) will review their safety data and determine whether the study can safely proceed with the treatment of subjects ≥5 and <12 years of age. After 2 subjects ≥5 and <12 years of age have attained NE after LentiGlobin BB305 Drug Product infusion, the DMC will review their safety data and determine whether the study can safely proceed with the treatment of subjects younger than 5 years of age. Subjects <12 years of age may only be enrolled at sites with regulatory approval for the specified age range.

The study has 4 distinct stages, as follows.

**Stage 1:** Screening to determine eligibility for treatment

**Stage 2:** Autologous CD34+ cell collection, LentiGlobin BB305 Drug Product manufacture and disposition

**Stage 3:** Myeloablative conditioning (4 days of conditioning followed by at least 48 hours of washout) and infusion of LentiGlobin BB305 Drug Product (Day 1)

**Stage 4:** Follow-up, through engraftment and up to 24 months after drug product infusion

The goal during the follow-up period is to maintain hemoglobin (Hb) ≥9 g/dL. Transfusions should be avoided for Hb ≥9 g/dL, unless the need is medically justified (e.g., as a pre-requirement for surgery). It is recommended that subjects should receive red blood cell (RBC) transfusions for any Hb <7.0 g/dL, and for clinically symptomatic anemia, irrespective of Hb level.

Subjects will be permitted to restart chelation post-drug product infusion (based on their iron overload status; recommendations are provided in the study protocol).

Subjects will be followed in this protocol for a period of approximately 24 months after LentiGlobin BB305 Drug Product infusion. Thereafter, subjects will be asked to enroll in a separate long-term follow-up protocol that will assess safety and efficacy beyond Month 24 for a total of 15 years after drug product infusion.

### 1.2.2. Randomization Methodology

Randomization was not performed as this is a single treatment, open-label study.

### 1.2.3. Unblinding

Unblinding is not applicable to this open-label study.

### 1.2.4. Stopping Rules

The Sponsor may stop enrollment into the study at any time for safety reasons as outlined in the study protocol section 3.5.

### 1.2.5. Study Procedures

The schedule of events (SOE) to be performed is provided in the study protocol section 6.1.

### 1.2.6. Efficacy, Pharmacodynamic, and Safety Endpoints

#### 1.2.6.1. Efficacy Endpoints

The efficacy endpoints include the effects on the expression of disease-specific biological parameters and clinical events that will be measured as follows:

**Primary Endpoint**

- The proportion of subjects who meet the definition of "transfusion independence" (TI). TI is defined as a weighted average Hb ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion

**Secondary Endpoints**

- Characterization of subjects achieving TI:
  - Proportion of subjects who meet the definition of TI at Month 24
  - Duration of TI
  - Time from drug product infusion to achievement of TI
  - Weighted average Hb during TI
- Characterization of transfusion reduction (TR):
  - Proportion 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 2 years prior to enrollment
  - Annualized number and volume of pRBC transfusions from 12 months post-drug product infusion through Month 24 compared to the annualized number and volume of transfusions during the 2 years prior to enrollment
  - Time from drug product infusion to last pRBC transfusion
  - Time from last pRBC transfusion to Month 24
- Weighted average nadir Hb during the 2 years prior to enrollment compared to weighted average nadir Hb from 12 months post-drug product infusion through the Month 24
- Unsupported total Hb levels over time, including Month 6, Month 9, Month 12, Month 18, and Month 24
- Unsupported total Hb levels ≥10 g/dL, ≥11 g/dL, ≥12 g/dL, ≥13 g/dL, ≥14 g/dL over time, including Month 6, Month 9, Month 12, Month 18, and Month 24

- Characterization of use of iron chelation and/or therapeutic phlebotomy among all subjects:
  - Proportion of subjects who have not received iron chelation therapy for at least 6 months following drug product infusion
  - Time from last iron chelation use to last follow-up
  - Proportion of subjects using therapeutic phlebotomy and annualized frequency of phlebotomy use per subject following drug product infusion
- Evaluation of the change in iron burden over time, as measured by:
  - Change in liver iron content (LIC) by magnetic resonance imaging (MRI) at baseline to Month 12 and Month 24
  - Change in cardiac T2* on MRI at baseline to Month 12 and Month 24
  - Change in serum ferritin at baseline to Month 12 and Month 24
- Evaluation of health-related quality of life (HRQoL) over time including Month 12 and Month 24 as compared to baseline, using the following validated tools:
  - Pediatrics: Pediatric Quality of Life Inventory (PedsQL; parent general core and general core)
  - Adolescents: PedsQL (parent general core and general core) and EuroQol-5D (Youth version) (EQ-5D-Y)
  - Adults: EuroQol-5D (EQ-5D), Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), and Short Form-36 (SF-36) v2

**Exploratory Endpoints**

- Assessment of growth and puberty parameters (age appropriate), bone density, diabetes, endocrine evaluations, and neurocognitive development (pediatric subjects <18 years of age)
- Assessment of change in dyserythropoiesis
- Correlations of pre-treatment variables (e.g., drug product vector copy number [VCN]) with response (e.g., peripheral blood VCN, $HbA^{T87Q}$).
- Measures of health resource utilization (including annualized number of transfusions, number of hospitalizations, number of days hospitalized) from 12 months post-drug product infusion through Month 24, compared to the annualized corresponding parameters during the 2 years prior to enrollment
- Length of in-patient hospital stay from initiation of conditioning to discharge

#### 1.2.6.2. Pharmacodynamic Endpoints

**Secondary Endpoints**

- $\beta^{A\text{-}T87Q}$- globin expression over time including Month 6, Month 9, Month 12, Month 18, and Month 24, as measured by assessing the ratio of $\beta^{A\text{-}T87Q}$-globin to all β-like-globin-chains, and α-globin to all β-like-globins, in whole blood
  - Correlation of $\beta^{A\text{-}T87Q}$-globin expression at early time points post-drug product infusion to $\beta^{A\text{-}T87Q}$-globin expression at later time points, as well as clinical outcomes
- VCN in peripheral blood over time, including Month 6, Month 9, Month 12, Month 18, and Month 24.

**Exploratory Endpoint**

- Relationship between measures of myeloablation and pharmacodynamics and clinical outcomes

Additionally, exploratory methods may be used to evaluate pharmacodynamic endpoints.

#### 1.2.6.3. Safety Endpoints

**Secondary Endpoints**

- Success and kinetics of hematopoietic stem cell (HSC) engraftment
- Incidence of transplant-related mortality through 100 days and through 365 days post-drug product infusion
- Overall Survival (OS)
- Detection of vector-derived replication competent lentivirus (RCL) in any subject
- Monitoring of laboratory parameters
- Frequency and severity of clinical adverse events (AEs)
- Incidence of acute and/or chronic graft-versus-host disease (GVHD)
- The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.)

**Exploratory Endpoint**

- The number of subjects with clonal predominance (see protocol Section 6.2.18 for description of criteria for clonal predominance and clinical work-up of malignancy)

# 2. SUBJECT POPULATION

## 2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) population: All subjects who initiate any study procedures, beginning with mobilization by granulocyte colony stimulating factor (G-CSF) and/or plerixafor
- Transplant Population (TP): All subjects who receive LentiGlobin BB305 Drug Product
- Successful Engraftment Population (SEP): All subjects who have successful NE after LentiGlobin BB305 Drug Product infusion

The ITT population is the primary population for the analysis of safety parameters. The TP is the primary population for efficacy, pharmacodynamic, and transplant parameter endpoints (i.e., success and kinetics of engraftment, and incidence of transplant-related mortality through 100 days and through 365 days post-drug product infusion). Selected safety analyses will also be performed on the TP. The SEP will be used to provide supportive data for subjects who engraft.

## 2.2. Protocol Deviations

All protocol deviations will be presented in a data listing; major and minor deviations will be indicated.

Categorization of protocol deviations will be determined by a review of the protocol deviation data collected on the case report form (CRF). Determination of major/minor and categorization of each protocol deviation type will be made prior to database lock.

A listing of subjects with protocol deviations related to COVID-19 will also be provided.

# 3. GENERAL STATISTICAL METHODS

## 3.1. Sample Size Justification

No formal sample size calculations were done.

Conversion to TI for patients with TDT is not a spontaneous event. Therefore, the conversion of any subject in the study to TI would be attributable to the therapeutic effect of LentiGlobin BB305 Drug Product with a very high probability. Any appreciable proportion of subjects who become TI on the study would represent a clinically meaningful treatment effect, to be assessed against the morbidity of the procedure.

Approximately 23 subjects in total will be treated with drug product, at least 15 of whom must be ≥12 and ≤50 years of age (at least 5 of whom must be ≥12 and <18) [Cohort 1], and at least 8 of whom must be <12 years of age [Cohort 2]. Replacement subjects may be added if subjects are screen failures or withdraw prior to drug product infusion.

The proposed sample size in Cohort 1 is based on the premise that excluding a treatment effect of <30% with a high probability is of value (demonstrating with 97.5% confidence that ≥30% of subjects become TI). Moreover, a point estimate of the proportion of patients who become TI of at least 60% is considered clinically meaningful. This point estimate was selected based on the minimal criterion to be met in the studies and was supported as the minimal target based on discussions with key opinion leaders with expertise in the treatment of β-thalassemia. Therefore, among the proposed sample size of 15 treated subjects ≥12 and ≤50 years of age in Cohort 1, a point estimate for success of 60% is proposed (9 out of 15 subjects), which would yield a lower 1-sided 97.5% exact confidence bound of 32.3%, exceeding the 30% minimal criterion. Among the proposed sample size of 8 treated subjects <12 years of age in Cohort 2, a point estimate for success of 62.5% (5 out of 8 subjects) would yield a lower 1-sided 97.5% exact confidence bound of 24.5%.

## 3.2. General Methods

All outputs will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

This study is primarily descriptive in nature. Data will be presented by subject and summarized overall within each analysis population.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, standard deviation (SD), median, minimum, and maximum values will be presented. Descriptive summary statistics as well as 2-sided 95% confidence intervals (CI), as appropriate, will be presented on selected parameters, as described in the sections below. A 2-sided 95% CI will be calculated for the primary endpoint using the Clopper-Pearson exact method.

Confidence intervals for other data expressed as proportions will also be calculated using the Clopper-Pearson exact method.

Longitudinal data (collected serially over time on study and follow-up) will be presented by appropriate time intervals, such as monthly, quarterly, and so forth, depending on the nature of the data.

For purposes of calculations, a month will be defined as 365.25/12 (30.4375) days and a year as 365.25 days. For reporting by month, calculations should be rounded to the nearest day (i.e., the calculated value at 18 months, 547.2, would be rounded to 547 days).

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-drug product infusion and post-drug product infusion study days are numbered relative to the day of infusion, which is designated as Day 1.

## 3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using version 23.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (B3 2021).

## 3.4. Baseline Definitions

Two years of retrospective pre-study enrollment data will be collected for each subject in the study, so that each subject may serve as his/her own control for the parameters of pRBC transfusion requirements, weighted average nadir Hb concentrations, in-patient hospitalizations (number and duration). For these parameters, baseline will be annualized over the 2 years prior to study entry (date of informed consent). For pRBC transfusion requirements, there will be 1 baseline parameter, the average per year. For the number of in-patient hospitalization days (defined as hospitalization duration of at least 24 hours), in addition to the total number of hospitalizations in the 2 years prior to study entry, the baseline average per year will be calculated. For other efficacy parameters as well as for pharmacodynamics parameters, baseline will be defined as the most recent measurement prior to conditioning; the conditioning start date will be defined as the first date of busulfan administration. For safety parameters, including shifts in key laboratory parameters, the most recent value prior to mobilization will be used as the baseline assessment.

## 3.5. Methods of Pooling Data

For purposes of the summary tabulations, subject data will be pooled across all study sites. All data will be presented in data listings that will identify site.

## 3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

## 3.7. Multiple Comparisons/Multiplicity

Formal multiplicity adjustment will not be performed. It is expected that majority of the secondary and exploratory endpoints will demonstrate a positive effect of LentiGlobin BB305 Drug Product. There are multiple secondary endpoints, which will enable a more complete understanding of the clinical impact of therapy with LentiGlobin BB305 Drug Product.

Further, the sample size for this study is of necessity modest, therefore consistency of effect in secondary endpoints will add credibility to the results of the primary efficacy analysis.

## 3.8. Subpopulations

Depending upon the number of subjects enrolled per subgroup, analysis may be performed based on baseline characteristics such as region, race, and/or sex. Selected tables, including primary efficacy data, will be summarized by age group, defined as age at informed consent/assent: >=18, <18, <18 and >=12, <12, and >=12. Further stratification may also be employed: <6 and 6 to <12 years. Selected tables will be analyzed by TI status.

## 3.9. Withdrawals, Dropouts, Loss to Follow-up

Screen failures and subjects withdrawn from the study prior to drug product infusion will be replaced.

Subjects who enroll in the study but discontinue prior to drug product infusion should be followed for at least 30 days after any invasive study procedure (e.g., mobilization, liver biopsy) before withdrawal, and ongoing AEs should be followed for 30 days. Subjects who withdraw post-drug product infusion will be asked to complete the same assessments as specified in the Schedule of Events (SOE) for Month 24 (Early Termination Visit assessments) and will be asked to enroll in the long-term follow-up Study LTF-303.

## 3.10. Missing Data

### 3.10.1. Transfusion Information

If a subject is missing a pRBC volume (mL) when it is known a transfusion took place, but the number of pRBC units is reported, then the average volume per unit provided on the CRF will be substituted and normalized for subject weight in kg; if the average volume per unit is missing, then the volume will be set to 300 mL/unit. If the volume or unit is completely missing, the mean volume will be imputed as follows: If the missing blood volume is pre-infusion, the mean volume that patient has received in the 2 years prior to enrollment is imputed; if the missing blood volume was transfused after study drug infusion, then the imputed volume will be the mean volume that patient received between study drug infusion up to the transfusion; if no other transfusions have been given during this time frame, then the pre-study enrollment mean volume will be used.

Subjects must have a minimum of 12 months pre-study enrollment transfusion data available to be included in the analysis of reduction of transfusion requirements.

### 3.10.2. Partial Dates

When tabulating AE data, partial dates will be handled as follows: The AE end date will be imputed first, before the AE start date is imputed. For AE end dates, if the day is missing, it will be set to the last day of the month or the last follow-up date, whichever occurs first; if both the day and the month are missing, it will be set to December 31 or the last follow-up date, whichever occurs first; if the end date is completely missing, it will be set to the last follow-up date.

For AE onset dates, if the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study drug treatment (i.e., drug product infusion). In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of study drug treatment, except in cases where this will lead to a start date being after stop date. In these situations, the original rule will be applied. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study drug treatment. In this case, the event onset will be coded to the day of study drug treatment to conservatively report the event as treatment-emergent, except in cases where this would lead to a start date being after stop date. In these situations, the original rule will apply. A missing onset date will be coded as the day of study drug treatment, except when this would lead to a start date being after the stop date. In these situations, the start date will be set to the first day of the month of the AE end date.

Partial dates for concomitant medication (CM) will be handled as follows: The CM end date will be imputed first, before the CM start date is imputed. If the CM end date is completely missing, the last follow-up date will be imputed; if only the day of the CM end date is missing, the last day of the month will be imputed; if the month and day of the CM end date is missing, December 31$^{st}$ of the year will be imputed. The imputed CM end date will then be compared to the last follow-up date; if it is later than the last follow-up date, the last follow-up date will be imputed instead. If the CM start date is completely missing, the date before the informed consent will be imputed; if only the day of the CM start date is missing, the 1$^{st}$ day of the month will be imputed; if the month and day of the CM start date is missing, January 1$^{st}$ of the year will be imputed. If the imputed CM start date is after the (imputed) CM end date, the (imputed) CM end date will be imputed instead. Partial dates for iron chelation will be imputed in the same way except for the fact that a completely missing end date will not be imputed.

Partial dates for diagnosis of β-Thalassemia Major/TDT will be handled as follows: if the day of the month is missing, the onset day will be set to the first day of the month. If the onset day and month are both missing, the day and month will be assumed to be January 1. If imputation of partial date results in a date of diagnosis less than the date of birth, then the date of birth is used as the date of diagnosis; age at diagnosis will be zero for these subjects.

For partial hospitalization dates: if there are partial hospitalization dates (date admitted, date discharged) and the month and year of the admission and discharge dates are the same, then the duration of hospitalization is imputed as 1 day. If the month of discharge is after the month of admission and the day of discharge is missing, the day of discharge is set to the first day of the month. If the month of discharge is after the month of admission and the day of admission and the day of discharge are both missing, both days will be set to the first day of the month.

### 3.10.3. Missing Data Due to COVID-19

Due to the COVID-19 pandemic, non-essential hospital visits may be cancelled. Thus, for safety reasons subjects who are not required to visit clinical trial sites may miss scheduled visits for assessments per study protocol.

For the primary endpoint (TI) and related characterization of TI, when the Hb at the end of the 12-month period needed to confirm TI is not available given the visit has been cancelled due to COVID-19, the last observation carried forward method will be used to impute the missing value provided 1) the weighted Hb from $t_0$ up to the latest observed Hb is ≥9 g/dL, 2) the subject has at least 6 months of observed Hb from $t_0$ to last follow-up, and 3) the subject has remained off pRBC transfusions from $t_0$ to last follow-up. Missed scheduled visits prior to TI confirmation will not be imputed for the primary analysis. As a sensitivity analysis, the lowest value observed post $t_0$ will be used to impute any missing values during the TI period. The above imputation rules will only be applied if the success criterion for TI cannot be reached due to missing Hb data from COVID-19 for regulatory submission.

To minimize bias that may be introduced by imputation, missing information of endpoints other than TI and its related characterization will not be imputed.

## 3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. In most of cases, data used in summaries will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is post-drug product infusion data from an unscheduled or additional visit that falls within a pre-defined midpoint window, the data from the unscheduled or additional visit will be used in data summaries. For subjects with multiple evaluations within a visit window, the evaluation closest to the target visit date will be used.

Midpoint windows for hematology laboratory parameters are listed in Table 1.

**Table 1: Midpoint Windows for Hematology**

| Timepoint | | Follow-Up | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month: | | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 | M14 | M15 | M16 | M18 | M20 | M22 | M24 |
| Day: | | D30 | D60 | D90 | D120 | D150 | D180 | D210 | D240 | D270 | D300 | D330 | D360 | D420 | D450 | D480 | D540 | D600 | D660 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 46 | 76 | 106 | 136 | 166 | 196 | 226 | 256 | 286 | 316 | 346 | 391 | 436 | 466 | 511 | 571 | 631 | 691 |
| | End | 45 | 75 | 105 | 135 | 165 | 195 | 225 | 255 | 285 | 315 | 345 | 390 | 435 | 465 | 510 | 570 | 630 | 690 | * |

* Last visit day.

Midpoint windows for chemistry laboratory parameters are listed in Table 2.

**Table 2: Midpoint Windows for Chemistry**

| Timepoint | | Follow-Up | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month: | | M1 | M2 | M3 | M4 | M5 | M6 | M9 | M12 | M15 | M18 | M24 |
| Day: | | D30 | D60 | D90 | D120 | D150 | D180 | D270 | D360 | D450 | D540 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 46 | 76 | 106 | 136 | 166 | 226 | 316 | 406 | 496 | 631 |
| | End | 45 | 75 | 105 | 135 | 165 | 225 | 315 | 405 | 495 | 630 | * |

* Last visit day.

Midpoint windows for VCN and Hb fractions are listed in Table 3.

**Table 3: Midpoint Windows for VCN and Hb Fractions**

| Timepoint | | Follow-Up | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Month: | | M2 | M3 | M6 | M9 | M12 | M18 | M24 |
| Day: | | D60 | D90 | D180 | D270 | D360 | D540 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 76 | 136 | 226 | 316 | 451 | 631 |
| | End | 75 | 135 | 225 | 315 | 450 | 630 | * |

* Last visit day.

Midpoint windows for iron studies parameters are listed in Table 4.

**Table 4: Midpoint Windows for Iron Studies**

| Timepoint | | Follow-up | | | | | |
|---|---|---|---|---|---|---|---|
| Month: | | M3 | M6 | M12 | M15 | M18 | M24 |
| Day: | | D90 | D180 | D360 | D450 | D540 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 136 | 271 | 406 | 496 | 631 |
| | End | 135 | 270 | 405 | 495 | 630 | * |

* Last visit day.

Midpoint windows for immunological testing and RCL are listed in Table 5.

**Table 5: Midpoint Windows for Immunological Testing and RCL**

| Timepoint | | Follow-up | | | |
|---|---|---|---|---|---|
| Month | | M3 | M6 | M12 | M24 |
| Day | | D90 | D180 | D360 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 136 | 271 | 541 |
| | End | 135 | 270 | 540 | * |

* Last visit day.

Midpoint windows for hormonal testing, bone marrow assessment, hepcidin, erythropoietin, LIC MRI and Cardiac T2* MRI are listed in Table 6.

**Table 6: Midpoint Windows for Hormonal Testing, Bone Marrow Assessment, Hepcidin, Erythropoietin, LIC MRI and Cardiac T2* MRI**

| Timepoint | | Follow-up | |
|---|---|---|---|
| Month | | M12 | M24 |
| Day | | D360 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 541 |
| | End | 540 | * |

* Last visit day.

Midpoint windows for FACT-BMT and EQ-5D/EQ-5D-Y are listed in Table 7.

**Table 7: Midpoint Windows for FACT-BMT and EQ-5D/EQ-5D-Y**

| Timepoint | | Follow-up | | | | |
|---|---|---|---|---|---|---|
| Month | | M3 | M6 | M12 | M18 | M24 |
| Day | | D90 | D180 | D360 | D540 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 136 | 271 | 451 | 631 |
| | End | 135 | 270 | 450 | 630 | * |

* Last visit day.

Midpoint windows for PedsQL, SF-36,Performance Status and ISA are listed in Table 8.

**Table 8: Midpoint Windows for PedsQL, SF-36, Performance Status and ISA**

| Timepoint | | Follow-up | | | |
|---|---|---|---|---|---|
| Month | | M6 | M12 | M18 | M24 |
| Day | | D180 | D360 | D540 | D720 |
| Analysis Window (Day) | Start | ≥ 1 | 271 | 451 | 631 |
| | End | 270 | 450 | 630 | * |

* Last visit day.

## 3.12. Study Periods

Study period reporting will be used in AE and clinical laboratory summaries unless otherwise specified. The ITT population will be used for reporting, with study periods as follows:

- Date of Informed consent form (ICF) until date of initiation of mobilization (ICF to <M)*
- Date of initiation of mobilization until date of initiation of conditioning (M to <C)
- Date of initiation of conditioning until the date of NE (C to <NE)
- Date of NE to Month 24 Visit (NE to M24)
- Day 1 (date of LentiGlobin BB305 Drug Product infusion) to Month 24 Visit (D1 to M24)
- Date of Informed consent to Month 24 Visit (ICF to M24)*

* This period is excluded from laboratory assessments.

## 3.13. Interim Analyses

Interim analyses are planned in support of regulatory submissions. The timing of these analyses and the number of subjects included in each analysis will take into account input from regulatory agencies and applicable regulatory guidance.

## 3.14. Final Analyses

A final analysis will be performed per protocol when all subjects treated with LentiGlobin BB305 Drug Product complete the study.

## 3.15. Additional Data Review

Safety data are reviewed on an ongoing basis for signal detection, DMC meetings, and to support preparation of regulatory submission documents. Analyses of study data may also be performed for the purposes of internal data review, regulatory agency interactions, and updating the scientific community.

# 4. STUDY ANALYSES

## 4.1. Subject Disposition

A tabulation of the disposition of subjects will be presented, overall and stratified by investigational site, including the number who initiate mobilization, the number who initiate myeloablative conditioning, the number infused with LentiGlobin BB305 Drug Product, and the extent of data available. Tables and listings will be provided for subjects in each analysis data set. The number of subjects completing the study through Month 24 Visit and reasons for study discontinuation will be reported.

Summary tabulations will be produced for the ITT population, TP, and SEP if they differ; all summarized data will be supported by data listings.

## 4.2. Demographics and Baseline Characteristics

The following demographic and baseline characteristic factors will be summarized: age (at diagnosis, at time of first transfusion, when frequency of transfusions was established, when iron chelation began, at time of enrollment, and at drug product infusion), genotype, country of birth, race and ethnicity, splenectomized, and spleen size (if relevant). Any age stratification will be done according to age at informed consent.

Additional screening results to be summarized will include the following: echocardiogram status and left ventricular ejection fraction (LVEF) %, and LIC by MRI (mg/g), LIC by liver biopsy (mg Fe/g dry weight) and liver biopsy status.

In addition, baseline data from the 2-year retrospective collection (pRBC transfusion requirements, number of in-patient hospitalizations and durations) will also be summarized. Both the mean pRBC volume (mL/kg/year) as well as the mean pRBCs given (number/year) for the 2 years prior to enrollment, excluding pRBC transfusions due to an acute event, will be summarized. The weighted average nadir Hb concentrations will also be summarized.

Determination of additional α-globin gene mutations will be performed for all subjects enrolled. Once enrollment in the study is completed all samples will be sent as a single batch for analysis and results will be provided in data listings.

## 4.3. Mobilization, Conditioning and Infusion Details

Information to be tabulated for mobilization cycles includes:

- Number of mobilization cycles/subject (1 or 2)
- Number of apheresis procedures per mobilization cycle
- Average G-CSF (µg/kg) and plerixafor (mg/kg) used per subject per day; the closest weight prior to mobilization will be used
- Total blood volume processed during apheresis (mL) (per cycle)
- Average total blood volume processed during apheresis (mL) (for subjects with multiple cycles, total blood volume will be average across both cycles)

- Number of CD34+ cells collected (cells x 10^6/kg)
- Number of CD34+ cells sent for transduction (cells x 10^6/kg)
- Number of CD34+ cells sent for rescue (cells x 10^6/kg)

Data will be summarized descriptively overall and by splenectomy status. Additional parameters such as amount of anticoagulant, volume of anticoagulant in bag at end of collection, hematopoietic progenitor cells collected by apheresis (HPC-A) volume, and subject's total blood volume will be provided in listings.

Dosing details to be summarized include the following:

- Duration of hospitalization (from initiation of conditioning to post-drug product infusion discharge)
- Number of drug product lots infused
- Total number of infused CD34+ cells (Combined total number of cells if more than one drug product lot, cells x 10^6/kg).
- VCN of drug product (DP VCN; weighted average per subject if more than one drug product lot, and average per lot, c/dg)
- Percent lentiviral vector positive (%LVV+) cells of drug product (weighted average per subject if more than one drug product lot per subject, and average per lot)
- DP VCN/%LVV+ cells (weighted average per subject if more than one drug product lot, and average per lot)
- Day of NE (defined as the day on which the first of 3 consecutive absolute neutrophil count (ANC) laboratory values obtained on different days was $\geq 0.5\times10^9$/L after a post-drug product infusion value $<0.5\times10^9$/L). For NE, if ANCs are not collected on a day but the white blood cell (WBC) count is less than $0.75\times10^9$ cells/L, the ANC is considered to be $<0.5\times10^9$/L for the purposes of calculating day of neutrophil recovery.
- Day of platelet engraftment (defined as the first of 3 consecutive unsupported platelet counts of $\geq 20\times10^9$/L obtained on different days starting after platelet counts dropped to $<20\times10^9$/L post-drug product infusion while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period. In the rare case that a subject does not have any post-transplant value of $< 20 \times10^9$/L, the initial post-infusion nadir may be used as a post-transplant value of $< 20 \times10^9$/L based on clinical judgement.); to be summarized as a continuous measure as well as categorized into $\leq$30 days, >30 to $\leq$60 days, >60 days to $\leq$90 days, and >90 days
- Incidence of successful NE (achieving NE by Day 43 and not receiving back-up cells at any time during the neutropenic phase)
- Incidence of successful platelet engraftment (achieving platelet engraftment at any time during the study)

- Time from initiation of mobilization to drug product infusion

If a subject had multiple lots of drug product, the DP VCN, %LVV+ cells, and DP VCN/%LVV+ cells will be measured per lot then the fractions of (drug product dose per lot/total drug product dose of all lots) will be used as weight to calculate weighted average per subject.

The use of medications for myeloablative conditioning (busulfan as well as any prophylactic and empiric anti-convulsive, antifungal, and antibiotic treatments, and other supportive care usage for the preparative regimen) will be included in the data listing. For busulfan, the total dose infused in mg, average daily dose (mg/kg/day), and the individual and daily estimated average busulfan area under the curve (AUC) (µM*min) will be included in a data listing. For calculation of the average daily dose (mg/kg/day), the closest weight prior to conditioning will be used for analysis. The daily estimated average AUC is defined as the average AUC including both observed and derived AUC, where derived AUC is calculated as the average of the observed AUCs per busulfan dose multiplied by observed busulfan dose when AUC is missing. A table summary of the total dose (mg), the average daily dose (mg/kg/day), the daily estimated average AUC (µM*min), the number and percentage of subjects below, within or above the protocol defined AUC range (3800 to 4500 µM*min) and the number and percentage of subjects with Q6H and Q24H regimen will also be provided.

Transfusions of any blood products (platelets, pRBCs) will be reported in listings in addition to pRBC efficacy analysis. The volume of each type of blood product transfusion (mL/kg) will also be reported. The closest weight prior to the transfusion will be used for analysis. If the amount of transfusion is reported in 'units', volume will be calculated as indicated in Section 3.10.

## 4.4. Efficacy Evaluation

Statistical methods will be primarily descriptive in nature and will include point estimates and 2-sided 95% CIs as appropriate. All efficacy information will be presented in data listings in addition to descriptive summary tables. The TP will be used for primary conclusions of LentiGlobin BB305 Drug Product efficacy, with supportive analyses performed on the SEP if SEP differs from the TP.

### 4.4.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is TI. TI is defined as a weighted average Hb ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion, where:

- Calculation of time period of TI will start when subjects achieve an Hb ≥9 g/dL with no transfusions in the preceding 60 days
- To meet the initial TI criteria, the weighted Hb must be ≥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 ≥9 g/dL from that point forward, without receiving a pRBC transfusion

- A transfusion of pRBCs for a single acute event (e.g., surgery, trauma, parvovirus infection, or sepsis) will not be counted towards the definition of TI. For the calculation of the weighted Hb when an allowed transfusion has occurred, the Hb that triggered the acute pRBC transfusion would be carried forward for 60 days after the acute pRBC transfusion and Hb values during those 60 days would be imputed by the carried-forward value. Post 60 days, the actual Hb drawn would again be used in the calculation of TI. In the case there were more than one acute transfusion, the Hb that triggered the acute transfusion will be carried forward for 60 days or until next acute transfusion within 60 days. Then the Hb that triggered the next acute transfusion will be carried forward for another 60 days after the last acute transfusion. When determining TI among subjects with acute pRBC transfusions, a subject can still achieve TI within the 60 days of Hb imputation.

The weighted average Hb for determining TI will be defined as follows. Let $t_0$, $t_1$, $t_2$, … represent the consecutive time points for assessment of Hb, where $t_0$ denotes the time when Hb is first ≥9 g/dL with no transfusions in the preceding 60 days, and where the $t_i$ are continuing as long as no transfusions are given. Further, let $h_0$, $h_1$, $h_2$, … represent the Hb level at each of these time points. Then the weighted average Hb is defined as:

$$[(t_1-t_0)x((h_0+h_1)/2)+ (t_2-t_1)x((h_1+h_2)/2)+\ldots+ (t_k-t_{k-1})x((h_{k-1}+h_k)/2)]/(t_k-t_0)$$

where $t_k$ represents the time point such that $(t_k-t_0)$ represents at least 12 consecutive months

This calculation is invariant to the metric used for the time points, e.g., calendar dates or days from drug product infusion, since the consecutive differences in times would always be measured as a number of days. Note that the weighted average may be considered as an average AUC calculation for Hb. To determine if a subject remains TI beyond 12 months, the calculation of weighted average Hb will always start at $t_0$. If a subject loses TI status, defined as starting transfusion again or weighted Hb falls below 9 g/dL, a new $t_0$ will be identified to determine future TI status. The calculation of the duration of TI will begin with $t_0$.

The primary efficacy endpoint of TI will be analyzed as a point-estimate of the proportion of subjects achieving TI at any time during the study, with a 2-sided 95% CI calculated using the Clopper-Pearson exact binomial method. The success criterion will be the lower bound of this CI is ≥30% for Cohort 1. Subjects in the TP who discontinue prior to their Month 24 follow-up post-drug product infusion will be considered as failures unless TI was reached prior to discontinuation. If any subjects achieved TI then lost TI, sensitivity analysis may be performed counting lost TI as failures.

TI evaluable is defined as patients who have completed their parent study (i.e., 24 months of follow-up), or achieved TI, or won't achieve TI in their parent study. A subject is deemed 'will not reach TI in the parent study' if he/she is receiving chronic transfusions after 324 days (750 days – 14 × 30.4375 days) of follow-up (less than 14 months of follow-up in parent study), or if his/her Hb level never reached $t_0$ (Hb ≥9 g/dL with no transfusions in the preceding 60 days) by 385 days (750 days – 365.25 days) of follow-up.

Imputation on missing Hb assessments due to COVID-19 and the primary and sensitivity analysis will be performed as described in Section 3.10.3.

### 4.4.2. Analysis of Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be descriptively analyzed.

- Characterization of subjects achieving TI:
  - Proportion of subjects who meet the definition of TI at Month 24. Summary statistics and 2-sided 95% CI will be presented.
  - Duration of TI. (TI subjects only). Time to event analysis will be performed and simple summary statistics will be presented.
  - Time from drug product infusion to achievement of TI. (TI subjects only). Summary statistics will be presented.
  - Weighted average total Hb during TI. (TI subjects only). Summary statistics will be presented.

The duration of TI will be calculated for TI subjects only. It will be analyzed using Kaplan-Meier (KM) method. Time to event summary statistics including the median, 25th and 75th percentiles and 2-sided 95% CIs will be presented. The duration of TI begins with $t_0$ and ends at the time point when subject receives a transfusion or the weighted average Hb falls below 9 g/dL, whichever is earlier. If TI is maintained through all Hb assessments, the duration of TI will be censored at the last Hb assessment date.

- Characterization of TR:
  - The proportion of subjects with a reduction in annualized mL/kg pRBCs transfused from 12 months (365 days) post-drug product infusion through the Month 24 Visit of at least 50%, 60%, 75%, 90% or 100% compared to the annualized pRBC transfusion requirement during the 2 years prior to enrollment. These categories will be analyzed as point-estimates of the proportion of subjects meeting the respective definitions; 2-sided 95% confidence intervals will be included.
  - Annualized number and volume of pRBC transfusions from 12 months (365 days) post-drug product infusion through the Month 24 Visit compared to the annualized number and volume of transfusions during the 2 years prior to enrollment.
  - Time from drug product infusion to last pRBC transfusion.
  - Time from last pRBC transfusion to Month 24

A transfusion of pRBCs for a single acute event will not be counted towards the analysis of TR.

The percentage of subjects who have a reduction in transfusion requirements will be defined on a per subject basis, and that data will be classified into the predefined categories (<50%, ≥50%, ≥60%, ≥75%, ≥90%, and 100%) corresponding to the extent reduction in transfusion requirements. Any change in transfusion requirements will be determined by comparing the percent difference in annualized pRBC transfusion requirements between 12 months post-drug product infusion and the Month 24 Visit versus the baseline annualized transfusion requirement defined by the 2 years of pre-enrollment transfusion data. The weight at screening will be used in calculations of pRBC transfusion requirements during the 2 years prior to study enrollment. For

transfusions occurring post-drug product infusion, the weight at or closest to the date of transfusion will be used. If a subject should discontinue between 12 months post-drug product infusion and the Month 24 Visit, the available follow-up data will be used. For any interim analysis, time from last pRBC transfusion to last follow-up will be presented.

Time from drug product infusion to last pRBC transfusion and time from last pRBC transfusion to Month 24 will be summarized in a table using descriptive statistics and presented in a horizontal bar graph. While a pRBC transfusion for an acute event will not be considered as a pRBC transfusion, it will be marked on the bar graph. If there are no post-drug product infusion pRBC transfusions, time from drug product infusion to last pRBC transfusion will be considered 0 and time from last pRBC transfusion to Month 24 will be defined as the time of drug product infusion to Month 24. For subjects that achieved TI and then restarted chronic transfusions, the last pRBC transfusion prior to TI will be presented. For any interim analysis, last follow-up will be analyzed instead of Month 24 if subjects have not completed Month 24 visit. Transfusion support will be presented in figures.

A sensitivity analysis will be performed for transfusion requirement analyses using the lowest 12-month period in the 2 years prior to enrollment (dividing the 2 years prior to enrollment into 13 consecutive 12-month periods, then choosing the lowest 12-month period) as the baseline during the 2 years prior to enrollment.

- The weighted average nadir Hb during the 2 years prior to enrollment compared to weighted average nadir Hb from 12 months post-drug product infusion through the Month 24 Visit

Weighted average nadir Hb is defined as the most recent Hb prior to each pRBC transfusion, on the day of transfusion or within 3 days and, if there is a period of more than 60 days without transfusion, all Hb records between Day 61 and last follow-up or next transfusion (inclusive) will also be included. If multiple Hb values occur on the same day, the lowest value will be selected. A transfusion of pRBCs for a single acute event will be counted as chronic transfusion when deriving nadir Hb.

A sensitivity analysis will be conducted for transfusion requirement analyses and weighted average nadir Hb utilizing the time period of 6 months post-drug product infusion (Day 183) through the Month 24 Visit.

For interim analysis, transfusion requirements and the weighted average nadir Hb utilizing the time period of hospitalization discharge through last follow-up may also be performed.

- Unsupported total Hb levels over time, including Month 6, Month 9, Month 12, Month 18, and Month 24. 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. Summary statistics over time and boxplots of unsupported total Hb will be presented. This analysis will be presented by sex and by TI status and for the overall TP.
- Unsupported total Hb levels ≥10 g/dL, ≥11 g/dL, ≥12 g/dL, ≥13 g/dL, ≥14 g/dL over time, including Month 6, Month 9, Month 12, Month 18, and Month 24. Number and percentage of subjects with unsupported total Hb levels meeting the thresholds will be

summarized over time. This analysis will be presented by sex and by TI status and for the overall TP.

- Characterization of use of iron chelation and/or therapeutic phlebotomy among all subjects:
  - Proportion of subjects who have not received iron chelation therapy for at least 6 months following drug product infusion
  - Time from last iron chelation use to last follow-up
  - Proportion of subjects using therapeutic phlebotomy and annualized frequency of phlebotomy use per subject following drug product infusion

Summary statistics will be presented for the two endpoints above. Iron chelation and/or therapeutic phlebotomy use will also be presented in a by-subject listing.

- Evaluation of the change in iron burden over time, as measured by:
  - Change in LIC by MRI at baseline to Month 12 and Month 24
  - Change in cardiac T2* on MRI at baseline to Month 12 and Month 24
  - Change in serum ferritin at baseline to Month 12 and Month 24

The number and percentage of subjects with LIC <7 mg/g [1] and <5 mg/g [2]; cardiac T2* >20 msec [3]; serum ferritin <2247 pmol/L (1000 ng/mL) and <674 pmol/L (300 ng/mL) [4] will be summarized over time. Change in iron burden over time will be summarized using descriptive statistics and will also be presented in by-subject listings. LIC, cardiac T2*, and serum ferritin data will be presented graphically over time at the scheduled visits as box and whisker plots with connected medians and additionally by-subject. This analysis will be performed on TP subjects and by TI status.

- Assessment of health-related Quality of Life

Quality of life (QoL) assessments are collected at Screening, Month 3 (if available), Month 6, Month 12, Month 18, and Month 24 Visits. The QoL tool used for each age at enrollment is specified in Table 9. Subjects will use the same QoL tool that they were given upon enrollment until completion of their Month 24 Visit, even if they would also be eligible to change to a higher aged tool during the study.

**Table 9: Age-appropriate Validated HRQoL Tools**

| Age | PedsQL General Core | PedsQL Parent General Core | EQ-5D-Y (youth) | EQ-5D | SF-36v2 | FACT-BMT |
|---|---|---|---|---|---|---|
| 0-4 | | X | | | | |
| 5-11 | X | X | X (11 only) | | | |
| 12-17 | X | X | X | | | |
| 18-50 | | | | X | X | X |
| Recall | Past month | Past month | Today | Today | Past 4 weeks | Past 7 days |

**SF-36 Health Survey and PedsQL**

The SF-36 Health Survey items are classified into several domains: those of General Health (questions 1, 11a, 11b, 11c and 11d), Physical Functioning (questions 3a-3j), Role-Physical (questions 4a-4d), Role-Emotional (questions 5a-5c), Social Functioning (questions 6 and 10), Bodily Pain (questions 7 and 8), Vitality (questions 9a, 9e, 9g and 9i), Mental Health (questions 9b, 9c, 9d, 9f and 9h), and Reported Health Transition (question 2). The scoring of the SF-36 will be performed according to published literature. The domain score is obtained as the total of the item raw scores within the domain. A transformed domain scale from 1-100 is obtained by normalizing the raw score as follows:

$$\text{Transformed Scale} = 100 \times \{\text{Actual raw total score} - \text{Lowest possible score}\}/\text{Raw score range (theoretical)}$$

Certain items have the raw score reversed in order to make the directionality ("good to bad" direction) the same for all scores. Certain scores (items 7 and/or 8, and item 11a) have a final item value that is adjusted prior to summation.

The physical component summary (PCS) and mental component summary (MCS) scores are scored using norm-based methods.

The means and SDs used in scoring come from the 2009 general US population and the factor score coefficient comes from the 2009 general US population. A linear T-score transformation method is used so that both the PCS and MCS have a mean of 50 and an SD of 10 in the 2009 general US population.

Missing data will be handled according to published methods using the QualityMetric algorithms for Full Missing Score Estimation, which uses the mean value of all items answered to impute a missing value as long as at least 50% of the domain items have been answered, except for the Physical Functioning scale which uses an item response theory (IRT) and regression methodology.

The SF-36 subscale scores, PCS, MCS and the change from Screening (baseline) by visit will be tabulated by TI status. SF-36 information by subject will be provided in data listings. Summary tables will include the mean change from baseline, SD, median change from baseline, minimum, maximum, and 95% CI at each time point.

The PedsQL will be analyzed similarly. Data will not be pooled between adult and youth survey results.

**EQ-5D/EQ-5D-Y Health Questionnaire**

The EQ-5D/EQ-5D-Y self-report questionnaires are standardized instruments to measure health status in adults and youths and provide a simple descriptive profile and a single index value for health status. The questionnaires have 2 parts: a descriptive system that classifies subjects across 5 dimensions of QoL (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and a visual analog scale (EQ VAS Health Status). Each of the 5 dimensions is scored on a 3-level scale from 1 ("I have no problems/pain/anxiety/worry") to 3 ("I have a lot of problems/pain/anxiety/worry").

The EQ VAS Health Status is a standard vertical VAS marked from 0 (Worst Imaginable Health State) to 100 (Best Imaginable Health State) for subjects to rate their own current HRQoL state.

No imputation will be performed for missing values on the EQ-5D/EQ-5D-Y.

The responses for each of the 5 quality-of-life dimensions will be provided in a listing. Descriptive statistics will be provided for the actual and changes from baseline to on-study evaluation for VAS scores by TI status. Supportive figures plotting these summary statistics may be provided to aid in the visual interpretation of any improvements.

**FACT-BMT**

The FACT-BMT scale was designed to measure aspects of QoL in relation to bone marrow transplantation. It consists of the Functional Assessment of Cancer Therapy - General (FACT-G) and a Bone Marrow Transplantation Subscale (BMTS) to assess specific BMT-related concerns.

The scoring of the FACT-BMT will be performed according to published literature (McQuellon et al., 1997) and calculated using the scoring guide version 4. The FACT-G score is derived by summing 4 domains (Physical, Social/Family, Emotional, Functional) yielding a composite QoL score for each individual. (Higher scores indicate better QoL.) The 12 items included in the BMTS were constructed to be compatible with the FACT-G. The item format is the same as the FACT-G and consists of a Likert-type scale ranging from 0-4. Scoring procedures for the BMTS are similar to those used for the FACT-G and consist of summing the items (with reversed scoring for several items), which produces individual subscale scores and an overall score.

The FACT-BMT scores by visit will be tabulated by TI status, along with the change from baseline. FACT-BMT information by subject will be provided in data listings.

### 4.4.3. Analysis of Exploratory Efficacy Endpoints

- Assessment of growth and puberty parameters (age appropriate), bone density, diabetes, endocrine evaluations, and neurocognitive development (pediatric subjects <18 years of age).
- Assessment of change in dyserythropoiesis, by evaluating change from baseline as well as number and percentage of subjects within normal range, where applicable in the following parameters:
  - In blood: reticulocyte, nucleated RBC, serum transferrin receptor, hepcidin, hepcidin/ferritin ratio (defined as hepcidin (ug/L) divided by ferritin (pmol/L) if assessments are within 3 days of each other) and erythropoietin (EPO)
  - In bone marrow: morphology, cellularity, and myeloid:erythroid ratio

These endpoints will be evaluated by use of descriptive statistical methods and summary statistics for change over time, including 2-sided 95% CIs. The number and percentage of subjects with myeloid:erythroid ratio between 2 to 4, 3 to 4, and each cellularity status will be summarized over time. Serum transferrin receptor, reticulocyte and nucleated RBC will be presented in by-subject figures. All dyserythropoiesis related parameters (including the myeloid:erythroid ratio in original format) will be presented in by-subject listings. If sufficient bone marrow sample is available, sample may be archived and/or other research tests (genetic testing) may be performed, a listing will of genetic testing of these sample will be presented.

- Correlations of pre-treatment variables (e.g., DP VCN) with response (e.g., peripheral blood VCN, $HbA^{T87Q}$). Correlation analyses of the following pairs of variables will be considered
  - DP VCN vs PB VCN at Month 6
  - %LVV+ cells in drug product vs PB VCN at Month 6
  - Total cell dose vs $HbA^{T87Q}$ at Month 6
  - DP VCN vs $HbA^{T87Q}$ at Month 6
  - %LVV+ cells in drug product vs $HbA^{T87Q}$ at Month 6
  - DP VCN/%LVV+ cells vs $HbA^{T87Q}$ at Month 6
- Measures of health resource utilization (including annualized number of transfusions, number of hospitalizations, number of days hospitalized) from 12 months post-drug product infusion through Month 24 Visit, compared to the annualized corresponding parameters during the 2 years prior to enrollment. For interim analysis, the last follow-up will be used if the Month 24 Visit has not yet been reached. Summary statistics will be presented.
- Length of in-patient hospital stay from initiation of conditioning to discharge. Summary statistics will be presented.

### 4.4.4. Analysis of Other Clinical Measures

The following data will be listed:

- Pulmonary function testing (PFT) (including oxygen saturation, DLco; % predicted DLco) and PFT interpretation at Screening, Month 12, Month 24 and at any unscheduled visit. Change from baseline in PFT measures will also be included in the listing.
- Echocardiology results at Screening, Month 12 and Month 24, as well as any unscheduled results.

## 4.5. Pharmacodynamic Evaluations

Analyses will be conducted using the TP and SEP (if different), and will include summary tables with descriptive statistics, summary figures (all subjects, all values versus time on the x-axis), displaying the items below:

- $\beta^{A-T87Q}$- globin expression over time including Month 6, Month 9, Month 12, Month 18, and Month 24, as measured by assessing the ratio of $\beta^{A-T87Q}$- globin to all β-like-globins, and α- globin to all β- like- globins (i.e., all β [including $\beta^{A}$, $\beta^{E}$, and $\beta^{A-T87Q}$], γ, and δ chains), in whole blood
  - Correlation of $\beta^{A-T87Q}$-globin expression at early time points post-drug product infusion to $\beta^{A-T87Q}$-globin expression at later time points, as well as clinical outcomes

Hb fractions over time (including $HbA^{T87Q}$, HbA, $HbA_2$, hemoglobin E (HbE), and hemoglobin F (HbF), as relevant, calculated using ratio data from HPLC and total Hb), by-subject (g/dL) and overall summaries by timepoint (will include by-subject figures with all fractions for a given subject in 1 plot, with pRBC transfusions marked as vertical lines). The ratios and total Hb used to derive the fractions will also be included in a by-subject listing.

- $HbA^{T87Q}$ = $\beta^{A\text{-}T87Q}$-Globin to All β-Like-Globin-Chains*total Hb
- HbA = $\beta^{A}$-Globin to All β-Like-Globin-Chains*total Hb
- $HbA_2$ = δ-Globin to All β-Like-Globin-Chains*total Hb
- HbE = $\beta^{E}$-globin to All β-Like-Globin-Chains*total Hb
- HbF = (γG-Globin to All β-Like-Globin-Chains+γA-Globin to All β-Like-Globin-Chains)*total Hb

In addition, unsupported endogenous Hb fractions over time, which is defined as the sum of HbA, $HbA_2$, HbE, HbF as applicable without any acute or chronic pRBC transfusions within 60 days prior, will be summarized for the TP and by TI status.

For the Hb fraction analysis, the globin sample (within the midpoint visit window) and the hematology sample will be merged by date. If the dates match, this Hb will be selected, even if a transfusion occurs on the same date. If a globin sample exists but there is no corresponding hematology sample with the same date, then the sample will be merged with the closest Hb result with no transfusion in between. If there are multiple Hb records on the same date, the one with the lowest value will be used. If the selected Hb is not within a ±7 day window of the globin sample, the fraction will be footnoted in the data listings. A midpoint window will be applied for by visit summary tables and figures (see Table 3). If there are multiple fractions for a subject within a given midpoint window, an average of the fractions and Hb used to derive the factions will be calculated and used in summary tables and figures. Subgroup analysis may be performed by sex and age groups.

VCN in peripheral blood over time, including Month 6, Month 9, Month 12, Month 18, and Month 24. Summary statistics will be presented. Subgroup analysis may be performed by sex and age groups.

Relationship between measures of myeloablation and PK and PD parameters as well as further exploration of associations between gene transfer and expression parameters will be explained in a separate pharmacodynamic SAP.

## 4.6. Safety Analyses

All subjects starting mobilization (i.e., the ITT population) will be evaluated for safety. Results reported as incidence will be analyzed as proportions and 2-sided 95% CIs will be included as appropriate.

The safety of treatment will be summarized through the longitudinal evaluation of AEs, laboratory assessments, and physical examination findings. Analyses will be performed in the TP on rates of failure to engraft, rates of AEs attributed to the transplant procedure or preparation for the procedure.

Because the safety profile will be assessed for several different time intervals (see Section 3.12), there may be subjects in the ITT population who are not candidates for analyses during some of these intervals. For example, if a subject has conditioning-regimen related events and does not receive LentiGlobin BB305 Drug Product, that subject would not be considered in the analyses of safety data post-drug product infusion (i.e., Day 1 through Month 24 Visit).

### 4.6.1. Adverse Events

All AEs will be collected from informed consent through the Month 24 Visit for the ITT population, irrespective of severity grade or relationship to LentiGlobin BB305 Drug Product.

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). Some AEs reported to the Investigations SOC will be recoded to their synonyms under Blood and Lymphatic System Disorders.. The AE grade will be based on criteria as described in the study protocol section 6.2.19.3. The safety analyses will include evaluation of the incidence of all AEs and of treatment-emergent AEs by SOC and preferred term. The terminology "treatment-emergent" is reserved for events that occur during or after LentiGlobin BB305 Drug Product infusion. Summaries of related AEs to LentiGlobin BB305 Drug Product will be based on the Investigator's assessment; an assessment of 'Possibly Related' or 'Related' will be considered related to drug product. Adverse events will be summarized for those events that occur in the intervals mentioned in Section 3.12. For treatment-emergent AEs only the following periods will be assessed: "Day 1 to <NE", "NE to Month 24 Visit", and "Day 1 to Month 24 Visit".

The appropriate denominators for rates of events will consist of the number of subjects "at risk" in each time period interval (will exclude subject lost to follow-up or who died prior to the beginning of the period). Summaries will be provided for the following by period:

- Incidence of all AEs
- Incidence of all Treatment Emergent AEs
- Incidence of all serious AEs (SAEs)
- Incidence of all Treatment Emergent SAEs
- Incidence of Grade 3 or higher AEs
- Incidence of Grade 3 or higher Treatment Emergent AEs
- Incidence of all study drug product related AEs*
- Incidence of all study drug product related SAEs*
- Incidence of Grade 3 or higher AEs related to study drug product
- Incidence of all AEs related to Plerixafor
- Incidence of all SAEs related to Plerixafor
- Incidence of Grade 3 or higher AEs related to Plerixafor
- Incidence of all AEs by System Organ Class (SOC)

- Incidence of all AEs by Preferred Term (PT)
- Incidence of all AEs from informed consent to Month 24 visit by selected subgroups (sex, age at informed consent, race) (Period from ICF to Month 24 and Day 1 to Month 24 Visit only)
- Incidence of all AEs by maximum severity (overall and by selected subgroups: sex, age, race)
- AEs attributed to Mobilization/Apheresis**
- AEs attributed to Conditioning**
- SAEs attributed to Conditioning**
- Incidence of acute and/or chronic GVHD*

*Treatment-emergent
** Based on investigator attribution on CRF for events not related to study drug.

For AEs by maximum severity, subjects will be summarized for the worst grade in each period based on the AE start date of all reported events.

A by-subject listing for all AEs occurring on study will be provided, and in addition, by-subject listings will be provided for subject deaths, SAEs, and SAEs related to drug, and AEs related to drug product.

**Events Attributed to Mobilization/Apheresis**

AEs designated on the CRF as attributed to mobilization/apheresis (G-CSF and plerixafor) will be summarized.

**Events Attributed to Conditioning**

Busulfan intravenous (IV) is a cytotoxic drug that causes profound myelosuppression. Accordingly, subjects will experience intended hematologic events (e.g., neutropenia, thrombocytopenia, anemia) and expected non-hematologic events (e.g., mucositis [stomatitis], nausea, vomiting, alopecia, pyrexia) as a result of receiving busulfan IV. For the purposes of this protocol, these events, which are familiar to transplant physicians, may be considered by investigators as related to conditioning. AEs designated on the CRF to be attributed to conditioning will be summarized.

**Treatment-emergent Events of Interest**

Treatment-emergent events of interest including Human immunodeficiency virus (HIV) infection, autoimmune disease/immunogenicity/long latency hypersensitivity, infections, malignancies, and bleeding events will be summarized. Definitions are described in Section 6.

**Engraftment**

The incidence of NE and platelet engraftment failure will be calculated and tabulated. Day of NE and platelet engraftment will be plotted against drug product total cell dose and average daily busulfan AUC using a scatter plot. Day of platelet engraftment will also be plotted against drug product VCN and %LVV+ cells using a scatter plot. Correlation analyses will also be presented.

### Event of Insertional Oncogenesis

Number and percentage of subjects with insertional oncogenesis (e.g., myelodysplasia, leukemia, lymphoma), in which LVV-insertion is demonstrated as likely to have contributed to the root cause of the malignancy will be summarized. Details will be presented in a by-subject listing. Events of malignancies will be reviewed via bluebird bio safety governance process to determine the root cause and if any event meets the insertional oncogenesis endpoint.

## 4.6.2. Laboratory Data

Clinical laboratory values will be expressed using the International System of Units (SI), with the exception of hemoglobin summaries and figures which will use g/dL.

| **Hematology** | **Iron Studies** |
|---|---|
| Complete blood count (CBC) with differential[a] | Iron* |
| Platelet count | Ferritin* |
| Reticulocyte/Erythrocyte* | Serum transferrin receptor* |
| Reticulocyte* | Transferrin* |
| Nucleated RBCs* | |
| **Serum Chemistry and Liver Function** | |
| Sodium | Blood urea nitrogen |
| Potassium | Creatinine |
| Chloride | Glucose[b] |
| Bicarbonate | Calcium |
| Albumin | Phosphate |
| Total protein | Bilirubin (total and direct) |
| Alanine transaminase | Alkaline phosphatase |
| Aspartate transaminase | Lactate dehydrogenase |
| Gamma glutamyl transferase | |

[a] CBC RBC evaluation should include RBC count, Hb, hematocrit, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration (MCHC).

[b] Fasting glucose/insulin and Homeostasis Model Assessment index testing should be done at least every 6 months. Oral glucose tolerance test is required for any abnormal fasting glucose.

* Laboratory parameter evaluated for efficacy.

For central laboratory data from PPD, the reference ranges from PPD will be utilized. For local laboratory data, internationally accepted ranges published by the New England Journal of Medicine and the Mayo Clinic will be utilized. For purposes of this plan, these ranges are referred to as Global Reference Ranges (GRRs). Age-specific (age at assessment as applicable) and sex specific ranges (i.e., adult or pediatric, male or female) will be used to flag out of range values and to categorize into CTCAE (version 4.03) grades where applicable.

In addition, creatinine clearance will be derived if data are available.

Additional exploratory clinical laboratory tests include hormonal levels and immunological cell analyses. The number and percentage of subjects in low, normal, and high range for selective hormonal and immunologic testing parameters will be summarized over time.

Hematology and chemistry parameters will be assessed for potentially clinically significant (CS) criteria. Lab results that meet the potentially CS criteria will be listed and summarized based on study periods in Section 3.12. The potentially CS thresholds used are listed in Table 10.

**Table 10: Potentially Clinically Significant Criteria for Hematology and Chemistry Parameters**

| **Hematology** | **Test Name** | **Potentially CS – Low if Observed Value is:** | **Potentially CS – High if Observed Value is:** |
|---|---|---|---|
| | Leukocytes | $<3.0 \times 10^9$/L | $\geq 16 \times 10^9$/L |
| | Lymphocytes | $<0.8 \times 10^9$/L | $>12 \times 10^9$/L |
| | Neutrophils | $<1.5 \times 10^9$/L | $>13.5 \times 10^9$/L |
| | Monocytes | | $>2.5 \times 10^9$/L |
| | Platelets | $\leq 75 \times 10^9$/L | $\geq 700 \times 10^9$/L |
| | Hemoglobin | <6 g/dL | >16 g/dL |
| **Chemistry** | **Test Name** | **Potentially CS – Low if Observed Value is:** | **Potentially CS – High if Observed Value is:** |
| Hepatic | Alanine Aminotransferase | | ≥3 x ULN |
| | Aspartate Aminotransferase | | ≥3 x ULN |
| | Alkaline Phosphatase | | ≥3 x ULN |
| | Bilirubin | | ≥34.2 umol/L |
| Renal | Urea Nitrogen | | ≥10.7 mmol/L |
| | Creatinine | | ≥176.8 umol/L |
| Electrolytes | Sodium | ≤126 mmol/L | ≥156 mmol/L |
| | Potassium | ≤3 mmol/L | ≥6 mmol/L |
| Other | Glucose | ≤2.22 mmol/L | ≥9.71 mmol/L |

Shift tables which will indicate abnormally high or abnormally low (or both as applicable) changes in laboratory parameter grade based on CTCAE criteria from baseline will be performed using the most abnormal value in the following periods: date of initiation mobilization until date of initiation of conditioning, date of initiation of conditioning until the date of NE, date of NE through Month 24 Visit, Day 1 (date of LentiGlobin BB305 Drug Product infusion) through Month 24 Visit. The parameters included in the CTCAE shift tables are listed below.

| | | |
|---|---|---|
| Hematology | White blood cell count (WBC) | Both |
| | Neutrophils | Decrease |
| | Platelets | Decrease |
| | Lymphocytes | Both |
| Chemistry | Alanine aminotransferase (ALT) | Increase |
| | Aspartate aminotransferase (AST) | Increase |
| | Albumin | Decrease |
| | Alkaline phosphatase (AP) | Increase |
| | Calcium | Both |
| | Creatinine | Increase |
| | Gamma-glutamyl transpeptidase (GGT) | Increase |
| | Glucose | Both |
| | Phosphate | Decrease |
| | Potassium | Both |
| | Sodium | Both |
| | Total bilirubin (TBL) | Increase |
| Coagulation | International Normalized Ratio (INR) | Increase |

Laboratory values for selected hematology and chemistry parameters will be presented graphically. Box plots will be provided showing summaries of the scheduled visits for each parameter: platelets, leukocytes, nucleated RBC, reticulocyte/erythrocyte (%), absolute reticulocyte, erythropoietin, hepcidin, hepcidin/ferritin ratio, ANC, MCV, MCH, iron, transferrin, ferritin, serum transferrin receptor, creatinine, total bilirubin, AST, ALT, ALP, and lactate dehydrogenase (LDH) for TP. In addition, by-subject figures will be provided including a single subject for each parameter: Hb (pRBC transfusions noted), platelets (with platelet transfusions noted), and absolute reticulocyte (with phlebotomy noted).

All laboratory data will be provided in data listings. A subset listing will be presented for all subjects with any laboratory values ≥Grade 3 based on CTCAE version 4.03 criteria.

### 4.6.3. Vital Signs, Performance Status, and Physical Examination

Vital signs to be measured include systolic/diastolic blood pressure, pulse, respiration rate, and temperature, and will be performed in accordance with institutional standards, as per the SOE.

The actual value and change from baseline (defined as most recent value prior to mobilization) to each on-study evaluation will be provided in a listing for each vital sign.

Additionally, a summary table of the number and percentage of subjects with potentially CS vital signs parameters at Day 1 will be presented and will be stratified according to pre or post infusion. The following criteria will be used to determine potentially CS values:

| | **Potentially CS – Low if:** | | | **Potentially CS – High if:** | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Observed Value is:** | **AND** | **Decrease from Baseline is:** | **Observed Value is:** | **AND** | **Increase from Baseline is:** |
| Systolic Blood Pressure | <90 mmHg | | ≥20 mmHg | >160 mmHg | | ≥20 mmHg |
| Diastolic Blood Pressure | <50 mmHg | | ≥10 mmHg | >95 mmHg | | ≥10 mmHg |
| Heart Rate | <50 bpm | | ≥15 bpm | >120 bpm | | ≥15 bpm |

Abbreviations: CS=clinically significant.

The subject's performance status will be measured at the Screening Visit, at the Pre-conditioning Visit, and at every 6 months after drug product infusion. Karnofsky score and Lansky score will be assessed at multiple time points prior to drug product infusion, and at all scheduled follow-up visits. Individual and combined Karnofsky performance status and Lansky performance status will be summarized by visit for the TP and SEP, along with change scores from baseline, and will be presented for each subject in data listings.

Additionally, Tanner staging will be performed at screening and every 6 months after infusion during puberty, if relevant and presented in data listings.

All physical examination findings will be presented in a data listing.

### 4.6.4. Concomitant Medications and Procedures

Concomitant medications will be coded using the WHO Drug Dictionary. All concomitant treatments/procedures (including transfusions) will also be displayed in by-subject listings. Periods similar to the AE periods will be indicated, with the exception of an additional <ICF period.

### 4.6.5. Transplant-Related Mortality

Transplant-related mortality will be determined by the investigator and summarized for the following intervals: from Screening through 100 days post-drug product infusion, and from Screening through 365 days post-drug product infusion.

### 4.6.6. Overall Survival

Overall survival is defined as time from date of LentiGlobin BB305 Drug Product infusion (Day 1) to date of death. Overall survival will be censored at the date of last follow-up if subject is alive. A by-subject listing of time from Day 1 to date of death or censorship will be provided.

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### 4.6.8. RCL

Blood will be tested for RCL at Months 3, 6, 12, and 24. Results will be listed as RCL screen detected or not detected, and by co-culture assay as detected or not detected for each visit as appropriate (co-culture is only performed if screening result is positive), and summarized.

# 5. CHANGES TO PLANNED ANALYSES

All changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the associated interim or final CSR. Decisions to deviate from planned analyses will be documented at the time they are made.

Changes from Protocol (Version 6.0) to SAP (Version 5.0):

Changes from Previous SAP:

| Section Number | Section | Changes |
|---|---|---|
| 1.1.1 | Introduction | Updated that this SAP is based on protocol version 6.0, dated 10 June 2021. |
| 3.3 | Computing Environment | Update WHO Drug Dictionary with (B3 2021). |
| 3.10.2 | Partial Dates | Updated the "the date of data cut" to "the last follow-up date". |
| 3.11 | Visit Windows | Added Midpoint windows for ISA and updated Table 8 accordingly. |
| 4.3 | Mobilization, Conditioning and Infusion Detials | Updated "Time from initialization of mobilization to drug product infusion" to "Time from initiation of mobilization to drug product infusion" |
| 4.4.3 | Analysis of Exploratory Efficacy Endpoints | Added "If sufficient bone marrow sample is available, sample may be archived and/or other research tests (genetic testing) may be performed, a listing will of genetic testing of these sample will be presented." |
| 4.4.3 | Analysis of Exploratory Efficacy Endpoints | Added " DP VCN vs PB VCN at Month 6" in the section of Correlations of pre-treatment variables |
| 4.6.1 | Adverse Events | Removed "A listing of these recoded PTs will be provided". |
| 4.6.1 | Adverse Events | Added " Event of Insertional Oncogenesis Number and percentage of subjects with insertional oncogenesis (e.g., myelodysplasia, leukemia, lymphoma), in which LVV-insertion is demonstrated as likely to have contributed to the root cause of the malignancy will be summarized. Details will be presented in a by-subject listing. Events of malignancies will be reviewed via bluebird bio safety governance process to determine the root cause and if any event meets the insertional oncogenesis endpoint." |

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[redacted]

# 6. APPENDIX

| Events of Interest and Safety Endpoints | Search Strategy |
|---|---|
| HIV infection | MedDRA HLT = Acquired immunodeficiency syndromes, Retroviral infections |
| Autoimmune disease/immunogenicity/long latency hypersensitivity | MedDRA HLGT = Autoimmune disorders<br>MedDRA HLT = Autoimmunity analyses, Anaemias haemolytic immune<br>MedDRA PT = Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Chronic graft versus host disease, Chronic graft versus host disease in intestine, Chronic graft versus host disease in liver, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in lung, Graft versus host disease in skin, Transfusion associated graft versus host disease |
| Infections | MedDRA SOC = Infections and infestations |
| Malignancies | MedDRA SMQ = Malignant tumors, Malignant lymphomas, Myelodysplastic syndrome, Blood premalignant disorders |
| Bleeding events | MedDRA SMQ = Haemorrhages |
| GVHD | MedDRA PT = Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Chronic graft versus host disease, Chronic graft versus host disease in intestine, Chronic graft versus host disease in liver, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in lung, Graft versus host disease in skin, Transfusion associated graft versus host disease |

# 7. REFERENCES

[1] Cappellini, M.D., Cohen, A., Porter, J., Taher, A. and Viprakasit, V. eds., 2014. Guidelines for the management of transfusion dependent thalassaemia (TDT). Nicosia, Cyprus: Thalassaemia International Federation.

[2] Clinical Study Protocol LTF-303 Version 4.0

[3] Carpenter, J.P., He, T., Kirk, P., Roughton, M., Anderson, L.J., de Noronha, S.V., Sheppard, M.N., Porter, J.B., Walker, J.M., Wood, J.C. and Galanello, R., 2011. On T2* magnetic resonance and cardiac iron. Circulation, 123(14), pp.1519-1528.

[4] Majhail, N.S., Lazarus, H.M. and Burns, L.J., 2008. Iron overload in hematopoietic cell transplantation. Bone marrow transplantation, 41(12), pp.997-1003.

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ii. send us an email to PPD and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

**Required hardware and software**

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

**Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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