STATISTICAL ANALYSIS PLAN

A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of the β-Hemoglobinopathies (Sickle Cell Anemia and β-Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector (LentiGlobin BB305 Drug Product)

Protocol HGB-205

EudraCT No. 2012-000695-42

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Protocol Version and Date:	Version 7.0, 19 May 2016
Name of Test Drug:	LentiGlobin BB305 Drug Product
Phase:	Phase 1/2
Methodology:	Open-label, Safety, and Efficacy
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Analysis Plan Date:	22 May 2019
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APPROVAL OF STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

Title: **A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of the β-Hemoglobinopathies (Sickle Cell Anemia and β-Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector (LentiGlobin BB305 Drug Product)**

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TABLES INCLUDED IN THE TEXT

VERSION HISTORY

Version Number	Approval Date
Version 1.0	23MAR2016
Version 2.0	13MAR2017
Version 3.0	27JUN2017
Version 4.0	22MAY2019

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACS	Acute chest syndrome
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CBC	Complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria For Adverse Events
DLco	Carbon monoxide diffusing capacity
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma glutamyl transferase
GRRs	Global reference ranges
Hb	Hemoglobin
HSA	Human serum albumin
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
ICH	International Conference on Harmonisation
ISA	Integration Site Analysis
ITT	Intent-to-treat [population]
IV	Intravenous
LDH	Lactic dehydrogenase
LVEF	Left ventricular ejection fraction
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NE	Neutrophil Engraftment
PBL	Peripheral blood leukocyte
PT	Preferred term

Abbreviation	Definition
PTT	Partial Thromboplastin Time
pRBC	Packed red blood cell(s)
RBC	Red blood cell
RCL	Replication competent lentivirus
Rel Day	Relative study day
RV	Respiratory volume
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease
SD	Standard deviation
SEP	Successful engraftment population
SI	International system of units
SOC	System organ class
TBL	Total bilirubin
TDT	Transfusion-dependent β-thalassemia
TI	Transfusion independence
TLC	Total lung capacity
TP	Transplant population
TR	Transfusion reduction
VC	Vital capacity
VCN	Vector copy number
VOC	Vaso-occlusive crises
VOEs	Vaso-occlusive event
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-205, A Phase 1/2, Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects with β-Hemoglobinopathies (Sickle Cell Anemia and β-Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral $\beta^{A\text{-}T87Q}$-Globin Vector (LentiGlobin BB305 Drug Product). It is based on protocol version 7.0, dated 19 May 2016.

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 final clinical study report (CSR) for this trial.

An interim analysis of subjects with β-thalassemia major (also referred to as transfusion-dependent β-thalassemia [TDT]) was performed in support of the regulatory submission of a marketing authorization application (MAA) for LentiGlobin BB305 Drug Product for the treatment of TDT. The interim analysis was conducted when the last subject with TDT treated in Study HGB-205 completed their Month 24 Visit. Subjects with sickle cell disease (SCD) were not included in this interim analysis. This SAP is intended to be used for the interim analysis as well as the final analysis when the last subject for either indication has completed their Month 24 Visit as specified in the protocol or discontinued from the study. The SAP also includes additional statistical analyses that, in conjunction with those outlined in the current protocol, are designed to demonstrate the consistency of efficacy and safety results across multiple clinical studies. Any additional analyses outside of the current protocol will be detailed in Section 5 of this SAP.

1.1.2. Study Objectives

The primary study objective is to determine the safety, tolerability, and success of engraftment with an autologous CD34+ cell-enriched population that contains cells transduced with LentiGlobin BB305 lentiviral vector encoding the $\beta^{A\text{-}T87Q}$– globin gene and suspended in human serum albumin (HSA) (Albunorm™ 5%) (drug product) after conditioning with busulfan IV in subjects with severe SCD or TDT.

Secondary objectives are to:

- Quantify gene transfer efficiency and expression:
  - Evaluate expression of $\beta^{A\text{-}T87Q}$– globin in whole blood.
  - Quantify the hematopoietic chimerism resulting from treatment with drug product (vector copy number [VCN]).

- Measure the effects of transplantation with drug product on the expression of disease-specific biological parameters and clinical events, including the volume of blood transfusions for both severe SCD and TDT, and for subjects with severe SCD, the number of vaso-occlusive crises (VOCs) and acute chest syndrome (ACS) events in each subject compared with the 2-year pre-treatment period prior to informed consent.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a single arm, single site, single dose, Phase 1/2 study in subjects with severe SCD, or TDT [transfusion dependence is defined as having received at least 100 mL/kg/year of packed red blood cells (pRBCs) in each of the 2 years preceding enrollment].

The study will evaluate the safety and efficacy of autologous hematopoietic stem cell transplant (HSCT) using a CD34+ cell-enriched population that contains cells transduced with LentiGlobin BB305 lentiviral vector encoding $\beta^{A\text{-}T87Q}$-globin.

The study has 4 distinct stages, as follows:

Stage 1: Screening to determine eligibility

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

Stage 3: Myeloablative conditioning and infusion of LentiGlobin BB305 Drug Product

Stage 4: Follow-up, through engraftment and 24 months 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. Study Stopping Rules

See study protocol section 3.4.2.2 for stopping rules for this study.

1.2.5. Study Procedures

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

1.2.6. Safety, Efficacy, and Pharmacodynamic Parameters

The endpoints stated in the protocol are included, but additional analyses intended to allow consistent evaluation across multiple studies using LentiGlobin BB305 Drug Product to treat TDT or SCD have been added. These additional analyses are outlined in Section 5 of this SAP.

1.2.6.1. Safety Parameters

The safety endpoints are:

- Success and kinetics of hematopoietic stem cell (HSC) engraftment
- Incidence of transplant-related mortality through 100 and 365 days post drug product infusion
- Overall survival
- Detection of vector-derived replication competent lentivirus (RCL) in any subject
- Characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.
- Monitoring of laboratory parameters and frequency and severity of clinical adverse events (AEs)

1.2.6.2. Efficacy Parameters

The efficacy endpoints include the effects on the expression of disease-specific biological parameters and clinical events and differ for subjects with TDT and SCD. It was anticipated to have N=4 subjects with TDT and N=3 subjects with SCD at study's end.

Data for the N=4 subjects with TDT were included for the analysis in support of the MAA.

Efficacy Endpoints for Subjects with TDT:

Characterization of Transfusion Reduction (TR)

- Reduction of at least 50%, 60%, 75%, 90% or 100% in average annual pRBC transfusion volume from 6 months post-drug product infusion through last visit (compared to the average annual pRBC transfusion volume requirement during the 2 years prior to enrollment). Frequency of pRBC transfusions from 6 months post-drug product infusion through last visit (normalized to a 12-month period) compared to the annual frequency of transfusions during the 2 years prior to enrollment.
- Average annual pRBC transfusion volume (mL/kg/year) from 6 months post-drug product infusion through last visit, including change and percent change from the average annual transfusion volume during the 2 years prior to enrollment.
- Where available, weighted average nadir hemoglobin (Hb) from 6 months post-drug product infusion through last visit compared to weighted average nadir Hb during the 2 years prior to enrollment, where nadir is defined as:
  - Pre-treatment: most recent Hb level within 3 days prior to each pRBC transfusion.
  - Post-treatment:
    - most recent Hb level within 3 days prior to each pRBC transfusion, and
    - if there is a period of more than 60 days without transfusion, all Hb records between Day 61 and up to day of last visit or next transfusion (inclusive) will also be included.

Characterization of Transfusion Independence (TI)

- Proportion of subjects with TI, 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. See Section 4.5.1 for details on characterization of TI.
- Duration of TI.
- Time from drug product infusion to last RBC transfusion prior to becoming TI.
- Time from drug product infusion to TI.
- Weighted average nadir Hb during period of TI.

Endpoints for Subjects with SCD:

- Number of vaso-occlusive crises (VOC), acute chest syndrome (ACS) and vaso-occlusive events (VOEs), which includes both VOC or ACS, through 24 months post drug-product infusion compared to 2 years prior to enrollment.
- Evaluation of changes in the nature or frequency of the subject-specific main inclusion criteria, not described by the above bullet, including cardiac, neurologic, and bone.
- RBC transfusion requirements (measured in milliliters [mL] per kilogram [kg]) per year post-transplant compared to the 2 years prior to enrollment, adjusted for time, as applicable.

Exploratory Efficacy Endpoints (for TDT or SCD subjects):

- CCI [redacted]

[redacted].

Pharmacodynamic Parameters (for TDT or SCD subjects):

The pharmacodynamic endpoints of gene transfer efficiency and expression will be quantified by measurement of the following:

- Therapeutic globin expression, as measured by $Hb^{A\text{-}T87Q}$ in peripheral blood and the ratio of α-globin and to all β-like-globins.
- Vector copy number in cell populations from peripheral blood and, if collected, bone marrow.

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] with or without plerixafor) or bone marrow harvest.
- Transplant Population (TP): All subjects in the ITT population who undergo LentiGlobin BB305 Drug Product infusion.
- Successful Engraftment Population (SEP): All subjects who have successful neutrophil engraftment 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 the analysis of efficacy and pharmacodynamic parameters. The TP is also the primary population for transplant-related safety parameters (e.g., success and kinetics of engraftment and incidence of transplant-related mortality through 100 days and 365 days post drug product infusion) in the event that TP and ITT are not identical. The SEP will be used to provide supportive evidence for subjects who successfully engraft, defined as 3 consecutive absolute neutrophil count [ANC] laboratory values $\geq 0.5 \times 10^9$/L obtained on different days. If the populations are the same, separate analyses will not be performed.

2.2. Protocol Deviations

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

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Sample size was not determined by formal statistical methods, but by extent and availability of data.

3.2. General Methods

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

Summary tabulations will be produced for a subset of parameters identified in Section 4, with the remaining data reported in data listings. 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.

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.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned. Data will be presented by indication, and within indication by subject.

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, 547.88, would be rounded to 548 days).

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre- 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 descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or higher, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 or higher). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2016 or later).

3.4. Baseline Definitions

Two years of retrospective pre-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 (mL/kg, number of pRBC transfusions), VOC, ACS and VOEs (for SCD subjects) and number of in-patient hospitalizations/hospitalization days. Baseline will be defined as the average of the transfusion requirements per year or number of in-patient hospitalizations/hospitalization days per year, as relevant, over the 2 years prior to study

enrollment (date of informed consent). For other efficacy parameters as well as for pharmacodynamic parameters, baseline will be defined as the most recent measurement prior to conditioning for TDT subjects and the first measurement obtained during screening for SCD subjects. The conditioning start date will be defined as the first date of busulfan administration.

For safety, including key laboratory (hematology and chemistry) parameters, the most recent value prior to mobilization (subjects with TDT) or the first value during screening (subjects with SCD) will be used as the baseline assessment.

3.5. Methods of Pooling Data

Tabular summaries will report data by indication (SCD, TDT).

3.6. Adjustments for Covariates

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

3.7. Subpopulations

Due to small numbers of subjects, no analysis of subgroups will be performed.

3.8. Withdrawals, Dropouts, Loss to Follow-up

Subjects withdrawn from the study prior to conditioning (myeloablation) will be replaced. Subjects who begin conditioning but are subsequently withdrawn will not be replaced.

3.9. Missing, Unused, and Spurious Data

3.9.1. 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 standard volume per unit for that transfusion provided on the CRF will be substituted and normalized for subject weight in kg. If neither number of units nor volume is reported, then the imputed volume, for transfusions rendered before study drug infusion, will be the mean volume that the patient has received in the 2 years prior to enrollment. If the unknown blood volume was transfused after study drug infusion, then the imputed volume will be the mean volume that that patient received between study drug infusion and most recent study visit; if no other transfusions have been given during this time frame, then the pre-study drug mean volume will be used. If all volumes are reported in units and there is no standard volume per unit provided, then 300 mL/unit will be imputed.

After drug product infusion, subjects who do not have a documented Hb value for any period greater than 6 months will be analyzed as follows for TI: if the values before and after the gap are both ≥9 g/dL and there are no transfusions during the gap, they are evaluable for TI during this period. If either value is <9 g/dL, this period cannot be counted towards the definition of TI.

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

3.9.2. Partial Dates

When tabulating AE and concomitant medication data, partial onset/start dates 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 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 dug 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. For AE end dates, an event missing the day of the month will be set to the last day of the month, and an end date missing both day and month will be set to missing.

Partial dates for diagnosis of β-Thalassemia Major/TDT and SCD 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. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All 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 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 midpoint window, the evaluation closest to the target visit date will be used.

Midpoint windows for VCN, fraction data, and laboratory parameters (hematology, chemistry, and iron studies) are listed in Table 1.

Table 1: Midpoint Windows for VCN, Fraction Data, and Laboratory Data

Timepoint		Follow-Up										
Month:		M1	M2	M3	M4.5*	M6	M9	M12	M15	M18	M21	M24
Day:		D30	D60	D90	D135	D180	D270	D360	D450	D540	D630	D720
Analysis Window (Day)	Start	> 1	46	76	114	159	226	316	406	496	586	676
	End	45	75	113	158	225	315	405	495	585	675	776

*Only available for some subjects.

Windows for time course distributions of AEs and concomitant medications are based on the following time periods relative to drug product infusion:

- Date of informed consent until either date of initiation of mobilization (TDT subjects) or bone marrow harvest (SCD subjects).
- Date of initiation of mobilization/bone marrow harvest until date of initiation of conditioning.
- Date of initiation of conditioning until the date of neutrophil engraftment (NE).
- Date of NE through Month 24 Visit.
- Day 1 (date of drug product infusion) through Month 24 Visit.
- Date of informed consent through Month 24 Visit

Windows for time course distributions of clinical laboratory shift tables (shift categories defined by Common Terminology Criteria for Adverse Events [CTCAE] grade [version 4.03]) will include the same time periods but exclude date of informed consent to mobilization/bone marrow harvest and date of informed consent through Month 24 Visit. Reporting intervals for treatment-emergent AEs are defined in Section 4.4.1 (Adverse Events).

3.11. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.12. Interim Analyses

The efficacy and safety of drug product in subjects with TDT was analyzed when all subjects with TDT in HGB-205 completed the study (Month 24), to provide supportive data for the regulatory submission of a MAA for LentiGlobin BB305 Drug Product for the treatment of TDT. Data from subjects with SCD were not included in this TDT analysis.

3.13. Final Analyses

A final analysis will be performed per protocol when all subjects treated have either completed their Month 24 Visit or discontinued from the study.

4. STUDY ANALYSES

4.1. Subject Disposition

A tabulation of the disposition of subjects will be presented overall and by indication, including the number who initiate cell harvesting, the number who initiate myeloablative conditioning, and the number infused with LentiGlobin BB305 drug product. Tables and listings will be provided for subjects in each analysis data set. The number of subjects completing the study through their Month 24 Visit and reasons for study discontinuation will be reported.

4.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be reported in data listings.

The following demographic and baseline characteristic factors will be reported: age (age at diagnosis, at first transfusion, at starting regular transfusions, at starting iron chelation, at informed consent or assent, and at drug product infusion), specific SCD and thalassemia-related mutations (including mutations on both *HBB* alleles using both HGVS terminology as well as $\beta^{+}/\beta^{0}/\beta^{S}$ terminology, grouped by genotype and including any other thalassemia-related non-*HBB* genetic results), genotype category (non-β^{0}/β^{0}) mutation, country of birth, race, ethnicity, gender, and splenectomy (yes/no).

In addition, baseline data from the 2-year retrospective collection (pRBC transfusion requirements and/or SCD-related data, where applicable) will be reported. All available data from the retrospective data collection period will be listed by subject. The identification of SCD-related data is described in Section 4.5.4, and will be reported in a separate data listing. The mean total volume of pRBCs transfused in the 2 years prior to the date of consent will be listed by subject in mL/kg/year: calculations will utilize the weight closest to the transfusion (in absolute days). Other data to be reported from the 2-year retrospective data collection include the following where available:

- The Hb transfusion trigger (i.e., the Hb concentration that the investigator designated as the value that would "trigger" a pRBC transfusion during the 2 years prior to study enrollment) (TDT subjects only).
- Weighted mean nadir Hb concentrations (i.e., the Hb concentration that immediately preceded a pRBC transfusion within 3 days) during the 2 years prior to study enrollment (TDT subjects only).
- Iron chelation usage at informed consent.
- In-patient hospitalizations during the 2 years prior to enrollment. For SCD subjects, primary reason for hospitalizations was also reported by the investigator, such as due to pain crisis, stroke, and ACS etc. (see Table 2).

Additional Screening results to be listed will include the following:

- Hemolysis markers at Screening: reticulocyte count and %, total bilirubin, and lactate dehydrogenase (SCD subjects only).

- Echocardiogram status (normal, abnormal (not clinically significant [NCS]), abnormal (clinically significant [CS]), missing).
- Left ventricular ejection fraction (LVEF) %.
- Liver iron concentration (mg/g dry weight) and liver diagnostic method (biopsy and/or MRI and/or superconducting quantum interference device [SQUID]), Cardiac T2* measurement (ms).
- Cerebral MRA/MRI and/or doppler (SCD subjects only)
- Subjects who opted in for fertility preservation (Y/N/unknown).

4.3. Mobilization, Harvest, Transplant and Conditioning Details

For TDT subjects, information to be listed includes the following:

- Number of mobilization cycles/subject.
- Number of apheresis procedures performed per mobilization cycle.
- Number of subjects requiring bone marrow harvest for rescue.
- Average filgrastim (µg/kg) and plerixafor (mg/kg) used per subject per day; the weight at screening will be utilized.
- Number of nucleated cells collected (cells$\times 10^8$).
- Total blood volume processed during apheresis (mL)
- Number of CD34+ cells sent for transduction (cells$\times 10^6$/kg).
- Number of CD34+ cells sent for rescue (cells$\times 10^6$/kg).

For SCD subjects, information to be listed includes the following:

- Number of harvest procedures/subject.
- Number of nucleated cells collected (cells$\times 10^8$).
- Number of mono-nucleated cells collected (cells$\times 10^8$).
- Volume sent for transduction (mL).
- Volume sent for rescue (mL).
- Number of CD34+ cells sent for transduction (cells $\times 10^6$/kg).
- Number of CD34+ cells sent for rescue (cells $\times 10^6$/kg).

Dosing details to be listed include the following:

- Time in months from informed consent to drug product infusion.
- 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 (cells$\times 10^6$/kg). (Combined total number of cells if more than one drug product lot).
- VCN of drug product (average per subject if more than one drug product lot, and average per lot)
- Time to neutrophil engraftment (NE) (defined as the day on which the first of 3 consecutive ANC laboratory values obtained on different days was $\geq 0.5\times 10^9$/L after a post-transplant value $<0.5\times 10^9$/L).
  For NE, if ANCs are not collected on a day but the white blood cell (WBC) count is less than 0.75×10^9 cells/L, the ANC count is considered to be $<0.5\times 10^9$/L for the purposes of calculating time to neutrophil recovery.
- Time from Day 1 to platelet engraftment (defined as the first day of 3 consecutive platelet values $\geq 20\times 10^9$/L (TDT subjects) or $\geq 50\times 10^9$/L (SCD subjects) obtained on different days while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period).
  Subjects who were treated with G-CSF during the post-drug product infusion period, as identified by review of concomitant medications, will be footnoted in all tables describing engraftment parameters.

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 listed. For busulfan, the total dose infused (mg), the average daily dose (mg/kg/day), the daily AUC (μM*min), and average daily AUC will be reported in a by-subject listing; the weight used in busulfan calculations will be the weight immediately prior to the first conditioning cycle. Other conditioning medications will be reported as concomitant medications as indicated in Section 4.4.5.

The number of transfusions of any blood products (platelets, pRBC) prior to hospital discharge will also be reported, along with the volume of each type of blood product transfusion (in mL/kg). If the amount of transfusion is reported in 'units,' volume will be calculated as indicated in Section 3.9.1. The weight used in transfusion calculations will be the weight closest to the transfusion.

4.4. Safety Analyses

The safety of treatment will be analyzed through the longitudinal evaluation of AEs and laboratory assessments in the ITT population. Analyses will be performed in the TP on rates of failure to engraft, rates of infection, and adverse effects of the transplant procedure.

Since the safety profile will be assessed for several different time intervals relative to mobilization or bone marrow harvest, conditioning, and post-drug product infusion, 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 drug product, that subject would not be considered in the analyses of safety data post-drug product infusion.

4.4.1. Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables (overall and by indication) and data listings using system organ class (SOC) and preferred term.

Incidence of AEs will be summarized by SOC and preferred term (PT) using MedDRA. Some AEs reported to the Investigations SOC will be recoded to their synonyms under Blood and Lymphatic System Disorders. A listing of these recoded PTs will be provided. The relationship of AEs to LentiGlobin BB305 Drug Product will be based on the Investigator's assessment. For the assessment of relationship to study drug product, a classification of 'Possibly Related' or 'Related' will be classified as related to drug product.

Incidence of AEs will be summarized by the following periods:

- Date of informed consent until either initiation of mobilization (TDT subjects: ICF to M) or bone marrow harvest (SCD subjects: ICF to BM).
- Date of initiation of mobilization (TDT subjects: M to C) /bone marrow harvest (SCD subjects: BM to C) until date of initiation of conditioning.
- Date of initiation of conditioning until the date of NE (C to NE).
- Date of NE through Month 24 Visit (NE to M24).
- Day 1 (date of LentiGlobin BB305 Drug Product infusion) through Month 24 Visit (D1 to M24).
- Date of informed consent through Month 24 Visit (ICF to M24).

The terminology "treatment-emergent" would be reserved for events that occur during or after the drug product infusion (i.e. D1 through M24 visit period). For treatment-emergent AEs only the following periods will be assessed: "D1 to <NE", "NE to M24 Visit", and "D1 to M24 Visit". For AEs in which there is ambiguity as to whether it was treatment-emergent, it will be conservatively ascribed as treatment-emergent.

For the above periods, the appropriate denominators for rates of events would consist of the number of subjects "at risk" in each interval. Summaries will be provided for the following by period:

- Incidence of all AEs
- Incidence of all serious AEs (SAEs)
- Incidence of Grade 3 or higher AEs
- Incidence of all study drug product related AEs*
- Incidence of all study drug product related SAEs*
- Incidence of all AEs by System Organ Class (SOC) frequency.
- Incidence of all AEs by maximum severity
- Incidence of all study drug product related AEs by maximum severity*
- AEs attributed to Mobilization/Apheresis (TDT) or BM harvest (SCD)**

- AEs attributed to Conditioning**

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

There was an administrative memo issued to clarify a change in adverse event collection in order to be aligned with the efficacy endpoints for sever SCD subjects only:

- ≥Grade 1 AEs: through 30 days after LentiGlobin BB305 Drug Product infusion;
- ≥Grade 2 AEs and SAEs: through 12 months after LentiGlobin BB305 Drug Product infusion;
- LentiGlobin BB305 Drug Product-related AEs: through 24 months after LentiGlobin BB305 Drug Product infusion;
- For SCD patients only: VOC and ACS must be reported throughout the study and regardless of the severity and/or the relationship with the LentiGlobin BB305 Drug Product:
  - For any events with 'pain' in the verbatim term, the investigator will be asked if this is related to a VOC to ensure we are capturing all VOC events;
  - [All events with pain in the verbatim were queried and none of those were determined as related to a VOC according to the investigator.]

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 product.

Events Attributed to Mobilization (TDT subjects only)

Toxicities associated with filgrastim and plerixafor may be considered by investigators as related to mobilization. AEs designated on the CRF as attributed to mobilization/apheresis will be summarized.

Events Attributed to Bone Marrow Harvest (SCD subjects only)

Toxicities associated with filgrastim and plerixafor may be considered by investigators as related to mobilization. AEs designated on the CRF as attributed to bone marrow harvest 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. All AEs designated on the CRF to be attributed to conditioning will be summarized.

Engraftment

The incidence of NE and platelet engraftment will be calculated and displayed in a summary table by indication. The relative day of NE and platelet engraftment will also be summarized using descriptive statistics as indicated in Section 4.3.

Neutrophil engraftment failure will be defined as not meeting the NE criteria by 42 days after drug product infusion (Day 43). A listing of subjects that are engraftment failures will be provided.

4.4.2. Laboratory Data

Laboratory data will be reported by local labs, except for Integration Site Analysis (ISA) data which will be reported by a specialty lab, Geneworks, and Replication Competent Lentivirus, which will be reported by a specialty lab, Genezen Labs. Clinical laboratory values will be expressed using the International System of Units (SI), with the exception of hemoglobin figures, which will be displayed using g/dL.

Internationally accepted ranges published by the New England Journal of Medicine and the Mayo Clinic are utilized. For purposes of this plan, these ranges are referred to as Global Reference Ranges (GRRs). Age-specific (age at informed consent/assent as applicable) and gender 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.

The versions of the GRRs being utilized for this study are as footnoted below. If updated GRRs are published during the course of the study, the version used will not be automatically updated.

Source	Version	Purpose
New England Journal of Medicine	2004;351:1548-63	Adult Ranges
Mayo Clinic	(As provided by bluebird bio on 04-AUG-2014)	Child Ranges

These sources along with any additional sources and/or additional ranges will be maintained in a separate document and provided as an appendix in the CRF.

The following clinical laboratory parameters are to be evaluated:

Hematology

- Complete blood count (CBC) with differential*
- Platelet count
- Reticulocyte count*
- Erythropoietin
- Prothrombin Time
- Partial Thromboplastin Time (PTT)

Iron Studies*

- Iron
- Ferritin
- Serum transferrin receptor
- Transferrin
- Iron saturation

Serum Chemistry and Liver Function

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Albumin
- Total protein
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)
- Gamma glutamyl transferase (GGT)
- Blood urea nitrogen
- Creatinine
- Glucose
- Calcium
- Phosphate
- Total bilirubin (TBL)
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LDH)
- Uric acid

* Laboratory parameter evaluated for efficacy. CBC parameters to be evaluated for efficacy include RBC, Hematocrit, and Hemoglobin.

Additional clinical laboratory tests may be performed at the investigator's discretion and will be listed. Urinalysis was performed as described in the SOE.

Shift tables which will indicate abnormally high or abnormally low 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 of mobilization (for TDT subjects) or bone marrow harvest (for SCD subjects) until date of initiation of conditioning, date 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.

Haematology	Haemoglobin (Hb) (SCD only)	Both
	White blood cell count (WBC)	Both
	Absolute neutrophils count (ANC)	Decrease
	Platelets	Decrease
Chemistry	ALT	Increase
	AST	Increase
	ALP	Increase
	Calcium	Both
	Creatinine	Increase
	GGT (SCD only)	Increase
	Phosphorus	Decrease
	Potassium	Both
	TBL	Increase

The parameters included in the CTCAE shift tables are Hb, ANC, platelets, WBC, serum creatinine, GGT, AST, ALT, TBL, ALP, calcium, phosphorus, and potassium.

Laboratory values for selected hematology and chemistry parameters will be presented graphically as appropriate. The following by-subject figures may be provided: reticulocyte count, ANC, iron, serum ferritin, serum transferrin receptor, transferrin, iron saturation, creatinine, total bilirubin, AST, ALT, ALP, and LDH. In addition, by-subject figures may be provided including

a single subject for each parameter: Hb (pRBC transfusions noted) and platelets (with platelet transfusions noted).

All laboratory data will be listed by indication and subject using descriptive statistics, with listings including change from baseline, where baseline is defined as the most recent value prior to mobilization (TDT subjects) or the first value during screening (SCD subjects), as well as results for immunological testing, serology and hormonal testing. A subset listing will be presented for all subjects with any laboratory values ≥Grade 3 based on CTCAE version 4.03 criteria.

4.4.3. Transplant-Related Mortality

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

4.4.4. Vital Signs, Karnofsky 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 Schedule of Events located in the protocol.

Karnofsky score for subjects ≥16 years of age will be assessed at multiple time points prior to drug product infusion, and at all scheduled follow-up visits along with change scores from screening and from time of drug product infusion.

Vital sign measurements, weight, change from Screening to each on-study evaluation of vital signs and weight, height, and Karnofsky performance status will be presented for each subject in data listings.

4.4.5. Concomitant Medications and Procedures

Concomitant medications will be coded using the WHO Drug Dictionary.

The use of concomitant medications will be included in a by-subject data listing. Periods similar to the AE periods will be indicated, with the exception of an additional <ICF period. Concomitant treatments/procedures (including transfusions) will also be displayed separately in listings. These listings will include iron chelator and phlebotomy use.

4.4.6. Overall Survival

Overall survival is defined as time from date of drug product infusion (Day 1) to date of death. Overall survival will be censored at the date of last visit if subject is alive. A by-subject listing of time from Day 1 to date of death or censorship will be provided by indication.

4.4.7. Integration Site Analysis

An ISA will be performed on peripheral blood leukocytes (PBLs) starting 6 months after the infusion of drug product, and more frequently if clonal dominance is suspected (see protocol for details).

The subjects who meet the ISA clonal dominance criteria at each applicable visit will be provided in a listing.

4.4.8. Replication Competent Lentivirus

Blood will be tested for RCL at Month 3, 6, 12, and 24 Visits. Results will be listed as RCL screen detected, detected but not quantified, and not detected, and by co-culture assays (if applicable) detected or not detected, for each visit by indication.

4.5. Efficacy Evaluation

Statistical methods will be primarily descriptive in nature. All efficacy information will be presented in data listings.

The efficacy analyses identified below will be performed on the TP unless otherwise specified.

4.5.1. Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)

The change from baseline (2 years prior to study enrollment) in pRBC transfusion requirements, as measured in both volume mL/kg and frequency (number of transfusions) will be calculated. The annualized change per subject from 6 months post-drug product infusion to Month 24 Visit will be reported in a listing according to indication.

The measurements of pRBC requirements will be annualized at the reporting intervals of 24 months, and last study visit post drug product infusion to account for variability in the number of days observed relative to Day 183 (6 months post-drug product infusion). Subjects will not be included in a time interval unless they have completed that visit. For the last study visit analysis, the day of the last available visit up to the Month 24 Visit (inclusive) will be used. For example, if a subject has only 23 months of observation post-drug product infusion (visit on Day 700), the standardized value at last visit will be defined as (*total volume*/(700-183))*365.25. The use of the actual visit day will also apply to derivations for the Month 24 Visit time interval analyses post-drug product infusion.

In addition to the standardized values, the actual number of transfusions and total volume pRBC at the time points above will be reported.

For all calculations of pRBC transfusion requirements, the weight at or closest to the date of transfusion will be used. The weight will be selected using the absolute value of the difference from the date of transfusion.

In addition, these data will also be presented as follows:

- List of treated subjects into categories as follows: <50%, ≥50%, ≥60%, ≥75%, ≥90% or 100% reduction in annualized pRBC transfusion volume from 6 months post-drug product infusion through last study visit (compared to the annualized pRBC transfusion volume requirement during the 2 years prior to enrollment). The day of the last available visit up to the Month 24 Visit (inclusive) will be used.
- Where available for subjects with TDT, weighted average nadir Hb during 2 years prior to enrollment and weighted average nadir Hb from 6 months post-drug product

infusion through the Month 12, 18, and 24 Visit and at last study visit will be compared. Nadir is defined as the Hb closest but within 3 days prior to a transfusion. Hb values on the day of the transfusion will be considered for nadir calculations; if multiple values occur on the same day, the lowest value will be selected. If no Hb fits these criteria, then no imputed Hb will be reported. Hemoglobin values prior to drug product infusion will not be used for imputation of missing Hb values after drug product infusion. If there is a period of more than 60 days without transfusion, all Hb records between Day 61 and up to day of last visit or next transfusion (inclusive) will also be included; if multiple Hb records occur on the same day, the lowest value will be selected.

- Where available for subjects with SCD, % HbS prior to each pRBC transfusion should be listed.
- Where available for subjects with TDT, the weighted average Hb nadir for the period 24 to 12 months prior to screening will be compared with the weighted average Hb nadir from 12 months prior to screening. If these values are not within 25%, a sensitivity analysis will be performed for change from baseline in pRBC transfusion requirements, as measured in both volume mL/kg/year and frequency (number of transfusions)/year. For this sensitivity analysis, baseline will be calculated from the 12 month period with the lower Hb nadir value. Post-baseline calculations will be the same as the primary analyses. Where available, Hb values for the 2 years prior to study enrollment (date of informed consent) will be listed, along with date of measurement and date of any pRBC transfusions that occurred, with Hb nadir values indicated.

4.5.2. Characterization of Transfusion Independence (subjects with TDT only)

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 transfusion would be carried forward for 60 days 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.

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 subjects who meet the definition of TI overall and (separately) at Month 24 Visit will be provided in a listing, along with the following parameters:

- Duration of TI.
- Time from drug product infusion to last pRBC transfusion prior to becoming TI.
- Time from drug product infusion to TI.
- Weighted average Hb nadir during the period of the most recent TI.

CCI [redacted]

4.5.4. Sickle Cell Disease Related Parameters (subjects with SCD only)

Sickle cell disease-related parameters will be collected as described in Table 2 and provided in a listing. For all event types, the source to identify events prior to consent will be the Medical History and Hospitalization Prior to Screening forms. The forms used to identify events post-consent are listed below by event type.

Table 2: SCD-Related Events

Event Type	CRF Forms to Identify Events Post Consent
VOC	AE/SAE, Hospitalization (Pain crisis per investigator)
ACS	AE/SAE, Hospitalization (ACS per investigator)
VOEs	AE/SAE, Hospitalization (VOC+ACS per investigator)
Significant Cerebral Abnormality (MRA/MRI), stroke	AE/SAE, Hospitalization (Stroke per investigator), MRA/MRI, transcranial doppler or CT head (additional assessment visit)
Cardiac function	Cardiac MRI, echocardiography

Note:
For events from AE CRF page, ACS= PT of "acute chest syndrome", VOC= PT of "sickle cell anemia with crisis" or pain related events as determined as VOC-related by investigator as indicated in verbatim term.
Stroke: all hospitalization for which primary reason for hospitalization is indicated by investigator as being due to stroke.

The SCD-related events post-drug product infusion through Month 24 Visit and last study visit will be reported, along with these events reported in the 2 years prior to enrollment. In addition, the number of events over each reporting interval will be converted to a yearly average and compared to the yearly average obtained for the 2 years prior to study enrollment, as appropriate. While converting to a yearly average, the number will be standardized for each reporting interval to account for variability in the number of days observed. For example, if a subject has only 9 months of observation (visit on Day 279), the standardized number of VOC events at 12 months will be defined as (*number of events*/279*)**365.25). These data will be listed for each SCD subject.

Changes in SCD-specific laboratory tests from baseline values will be summarized for hemolysis markers (e.g., reticulocyte count, total bilirubin, and lactate dehydrogenase) as part of the laboratory reporting in Section 4.4.2.

Primary reason for hospitalizations, such as pain crisis, acute chest syndrome, stroke, infection or other, will be presented. The annualized rates in the 2 years prior to enrollment will be compared to the annualized rate post discharge after transplantation to the last study visit, as appropriate, where the admission date > date of discharge from the Hospital Admission CRF.

CCI [redacted]

4.5.8. Other Clinical Measures (subjects with TDT or SCD)

The following data will be listed:

- Pulmonary function testing (PFT) (Including oxygen saturation, FVC; FEV_1; TLC; RV, VC; and DLco; % predicted FVC, % predicted FEV_1; % predicted RV; and % predicted DLco (corrected for Hb) at Screening and at any unscheduled visit. Change from baseline in PFT measures will also be included in a listing for subjects with SCD.
- Echocardiography results at Screening and Month 24.
- SCD-specific testing.

4.6. Pharmacokinetic and Pharmacodynamic Evaluations

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

- The VCN post drug product infusion in cell populations from peripheral blood or whole blood. Bone marrow and lineage cells will be included in a listing only, if available; peripheral or whole blood VCN over time (TDT or SCD subjects in 1 figure)
- The ratio of α-globin to all non-α-globin-chains (i.e., including all β, γ, and δ chains) and ratio of α-globin to all β-globin-chains (i.e. β^A, β^E, and $\beta^{A\text{-}T87Q}$ chains) in whole blood (HPLC data, tabulated overall and by subject). (TDT subjects)
- Hemoglobin A^{T87Q} (HbA^{T87Q}) (g/dL) over time (table and TDT or SCD subjects in 1 figure).
- Hemoglobin fractions over time (including HbA^{T87Q}, HbA, HbA_2, HbE (for TDT subjects only), HbS (for SCD subjects only) and 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 one plot). 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/100*total Hb
  - HbA = β^A-Globin to All β-Like-Globin-Chains/100*total Hb
  - HbA_2 = δ-Globin to All β-Like-Globin-Chains/100*total Hb
  - HbE = β^E-Globin to All β-Like-Globin-Chains/100*total Hb
  - HbS = β^S-Globin to All β-Like-Globin-Chains/100*total Hb
  - HbF = (γG-Globin to All β-Like-Globin-Chains+γA-Globin to All β-Like-Globin-Chains)/100*total Hb

For the Hb fraction analysis, the globin chain sample will first be merged with the Hb hematology sample by date. If a globin chain sample exists but there is no corresponding hematology sample with the same date, then the sample will be merged with a hematology record whose sample date is within 7 days prior to the globin chain sample. If there are multiple hematology records within the 7-day window, the one closest to the globin chain sample will be

used. If there are multiple Hb records on the same date, the one assigned with the scheduled visit will be used. If there is no hematology record within the 7-day window, the one closest to the globin chain sample will be used, with a footnote in data listings. In addition, any globin chain samples with a pRBC transfusion within 30.4375 days prior should be noted in the data listings. The Hb fractions can then be derived as defined above. Note that when calculating Hb, values should first be converted to g/dL. A midpoint window will be applied for by-visit summary tables and figures (see Table 1). Within a given midpoint window for a particular subject, if there are multiple fraction results, an average will be calculated.

5. CHANGES TO PLANNED ANALYSES

All major changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the study report. Decisions to deviate from planned analyses will be documented at the time they are made.

The table below identifies changes from SAP (V3.0) to this version, SAP (V2.0) to SAP (V3.0), SAP (V1.0) to SAP (V2.0), and the protocol defined analyses to SAP (V1.0).

Major changes between SAP Version 3.0 and Version 4.0

Section Number	Section	Changes from Prior SAP Version
1.2.6.2	Efficacy Parameters	Further defined efficacy/exploratory endpoints for SCD subjects, to be aligned with Study HGB-206.
3.2	General Methods	Removed Excel files as a formal output format.
3.4	Baseline Definition	Refined baseline definition for SCD subjects, to be aligned all SCD studies.
3.5	Methods of Pooling Data	Dropped pooled analyses of TDT and SCD indications, given the fact that the small sample size for both indications is relatively small.
4.2	Demographic and Baseline Characteristics	• Further clarified what baseline data to be presented for SCD subjects. • eGFR at baseline was dropped since this analysis was not conducted for TDT subjects, and it is not a critical analysis for SCD subjects either.
4.4.1	Adverse Events	• Further clarified AE analysis/reporting periods for SCD subjects. • Removed analyses towards event of interest since it was deemed less applicable to this drug product and it was not conducted for interim CSR.
4.4.2	Laboratory Data	• Further clarified the source of lab data. • Added GGT and LDH to shift table for SCD subjects; also clarified Hb shift table is intended for SCD subjects only. • Dropped eGFR wording as the analysis was removed from baseline.

Section Number	Section	Changes from Prior SAP Version
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Removed timepoint Month 6, 18 from the planned analysis, since the analyses were not conducted for TDT subjects, and it is sufficient to report data at Month 24 for SCD subjects.
4.5.4.	Sickle Cell Disease Related Parameters (subjects with SCD only)	Further refined SCD-related endpoints and analyses per data collected on eCRF.
4.5.7	CCI [redacted]	[redacted]
4.5.8.	Other Clinical Measures (subjects with TDT or SCD)	Further defined analyses related SCD subjects.
4.6	Pharmacokinetic and Pharmacodynamic Evaluations	Further defined analyses pertaining to SCD subjects.
5	Changes to Planned Analyses	Added major changes from SAP (V3.0) to this version.

Changes between SAP Version 2.0 and Version 3.0

Section Number	Section	Changes from Prior SAP Version
1.1.1	Introduction	Changed interim analysis timing from 18 to 24 months.
1.2.6.2	Efficacy parameters	Limited Hb nadir definition to only consider Hb values within 3 days prior to pRBC transfusion.
1.2.6.2	Efficacy parameters	Removed 18-month summaries
1.2.6.2	Efficacy parameters	Added 'Time from drug product infusion to TI'
1.2.6.2	Efficacy parameters	Added 'Weighted average nadir Hb during period of TI
2.1	Population definitions	Specified TP as primary population for pharmacodynamics parameters.
2.1	Population definitions	Clarified neutrophil successful engraftment definition (3 consecutive values values ≥0.5×109/L obtained on different days).
3.2	General Methods	Modified year and month calculations to 365.25 days and 365.25/12 (40.4375) respectively.
3.9.1	Transfusion Information (TDT Subjects)	Added imputed value of 300 mL/unit when there all volumes reported in units and there is no standard volume per unit provided.
3.10	Visit Windows	Added midpoint visit windows to assign reporting periods for use in summarizations. These windows apply to VCN, fraction data, and unscheduled laboratory visits.
3.10	Visit Windows	Add new reporting period: Date of informed consent to Month 24.
4.1	Subject Disposition	Remove tabulation at Month 18.
4.2	Demographic and Baseline Characteristics	Removed summary of ongoing medical history and time from diagnosis to both informed consent and drug product infusion.
4.2	Demographic and Baseline Characteristics	Specify that the baseline calculation for pRBC transfusions (mL/kg/year) will use the weight closest to the transfusion (in absolute days).

Section Number	Section	Changes from Prior SAP Version
4.3	Mobilization, Transplant, and Conditioning Details	Clarified filgrastim and plerixafor reporting: Average filgrastim (µg/kg) and plerixafor (mg/kg) used per subject per day; the weight at screening will be utilized.
4.3	Mobilization, Transplant, and Conditioning Details	Dosing details, remove the following: • Time in months from diagnosis of β-hemoglobinopathy type … • Incidence of use of back-up cells for subjects with neutrophil engraftment failure.
4.3	Mobilization, Transplant, and Conditioning Details	Clarified VCN and CD34+ cell summaries if more than one drug product lot used.
4.3	Mobilization, Transplant, and Conditioning Details	Change busulfan reporting and added average daily AUC
4.4.1	Adverse Events	Added summary period for all AE reporting: date of informed consent through Month 24 visit.
4.4.1	Adverse Events	Add specific treatment-emergent AE reporting periods: Day 1 to < NE, NE to Month 24 Visit, and Day 1 to Month 24 Visit.
4.4.1	Adverse Events	New AE tables added: Events of Interest, Adverse Events by System Organ Class Frequency, Adverse Events by Reporting Period and Maximum Grade.
4.4.2	Laboratory Data	Indicated efficacy labs
4.4.2	Laboratory Data	Clarify Hemoglobin will not be presented in SI, but rather as g/dL for figure displays
4.4.2	Laboratory Data	Added by subject figures for iron studies
4.4.2	Laboratory Data	Removed mobilization figures and, for adolescents, figures for hormonal results.
4.4.2	Laboratory Data	Clarified ≥Grade 3 CTCAE listing applies to all parameters using CTCAE grading.
4.4.5	Concomitant medications	< ICF period added for reporting.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD).	Changed 30.4 to 30.4375 and adjusted Month 6 to Day 183. Change text to "Day 183 (Month 6 post-drug product infusion).
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD).	Clarified that use of actual Visit day is used for derivations for Months 12, 18 and 24 comparisons; last study visit analysis will use the last visit available up to Month 24 Visit (inclusive)
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD).	Add "<50%" to pRBC transfusion volume reporting (baseline to last visit). Also clarified last study visit analysis will use the last visit available up to Month 24 Visit (inclusive)
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD).	Nadir definition updated to use a 3-day window for Hb prior to transfusion. Hb values on the day of the transfusion will be considered for nadir calculations; if multiple values occur on the same day, the lowest value will be selected

Section Number	Section	Changes from Prior SAP Version
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD).	Added a sentence: If there is a period of more than 60 days without transfusion, all Hb records between Day 61 and last visit or next transfusion (inclusive) will also be included. If multiple Hb records occur on the same day, the lowest value will be selected.
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Synchronized definition with other LentiGlobin studies.
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Added reporting of time from drug product infusion to TI
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Added reporting of weighted average Hb nadir during the period of the most recent TI
4.5.3	CCI [redacted]	[redacted]
4.5.6	Pharmacokinetic and Pharmacodynamic Evaluations	Added clarity on fraction derivation analysis. Added ratios to the analysis.

Changes between SAP Version 1.0 and Version 2.0

Section Number	Section	Changes from Prior SAP Version
1.1.1	Introduction	Have removed descriptive text regarding indication and drug product. Modified header to “Introduction”
1.2.1	Synopsis of Study Design	Shortened text
1.2.4	Study Stopping Rules	Shortened text and referenced protocol section.
1.2.5	Study Procedures	Shortened text and referenced protocol section.
1.2.6	Safety, Efficacy, and Pharmacodynamics Parameters	Reordered presentation to start with Safety in alignment with the protocol.
1.2.6.1	Safety Parameters	Removed the safety endpoint "Characterization of events of insertional mutagenesis leading to clonal dominance or leukemia"”
1.2.6.2	Efficacy Parameters	Replaced endpoint of reporting from ‘Month 18 (or later as applicable’ to ‘last visit’.
1.2.6.2	Efficacy Parameters	Specified ‘weighted’ mean nadir Hb concentrations for reporting.
1.2.6.2	Efficacy Parameters	Removed the efficacy endpoints: Transfusion free survival, Description of markers of dyserythropoiesis, by subject, as measured in blood and bone marrow, Number of total in-patient hospitalization days (post-transplant discharge) at 6, 12, 18, and 24 months.
1.2.6.3	Pharmacodynamic Parameters	Removed and reference to exploratory PD assessments, as they will be covered in a separate PD analysis plan.
2.1	Population definitions	Added successful engraftment population (SEP) for consistency with HGB-204

Section Number	Section	Changes from Prior SAP Version
3.2	General Methods	Removed time-to-event methods as it is no longer applicable to this study due to small number of subjects.
3.3	Computing Environment	Added MedDRA reporting version (19.0 or higher)
3.3	Computing Environment	Added World Health Organization (WHO) Drug Dictionary (March 2016 or later).
3.4	Baseline Definitions	For pRBC transfusion requirements, removed baseline average per month parameter due to current reporting requirements.
3.4	Baseline Definitions	Added number of in-patient hospitalizations / hospitalization days
3.4	Baseline Definitions	For safety parameters, changed baseline assessment from screening to the most recent value prior to mobilization.
3.9	Missing, Unused and Spurious Data	Moved specific rules for missing Hb values into Efficacy section (4.6.1) and removed text 'immediately prior to pRBC transfusion' for ease of reference.
3.9.1	Transfusion Information (TDT Subjects)	Removed use of 300 mL/unit if transfusion volume is missing and average volume per ml per site is missing. Replaced 300 mL/unit with average mean volume in 2 years prior to study (prior to infusion) and average mean volume post infusion to time of transfusion (post infusion).
3.9.2	Partial Dates	Added a new paragraph for handling partial hospitalization dates.
3.10	Visit Windows	Added table from protocol for visit windows, as protocol Schedule of Events was deleted from Section 1.2.5.
3.10	Visit Windows	Added text and table for midpoint visit windows, to be used in analysis of Hb fractions and VCN.
3.10	Visit Windows	Added reporting windows for adverse events, laboratory shift tables, and concomitant medications.
3.12	Interim Analysis	Clarified text to specify that TDT only subjects would be reported in the interim report for the MAA submission.
3.13	Final Analysis	Added section to clarify timing of final analysis.
4.1	Subject Disposition	Removed reporting by β-Thalassemia genotype.
4.1	Subject Disposition	Clarified reporting format for interim analysis.
4.1	Subject Disposition	Removed text for reporting deviations from protocol treatment, as described in Section 2.2.
4.2	Demographics and Baseline Characteristics	Explained the genotype and mutation categories in detail
4.2	Demographics and Baseline Characteristics	For retrospective data reporting added additional parameters: Number of total in-patient hospitalizations, total in-patient hospitalization days, number of ACS, VOC and SCD events.

Section Number	Section	Changes from Prior SAP Version
4.2	Demographics and Baseline Characteristics	Changed format of reporting to listings from summaries, removed specific categories of information (items I – VIII in Version 1.0 SAP) to be reported together.
4.2	Demographics and Baseline Characteristics	Added reporting of liver diagnostic method.
4.2	Demographics and Baseline Characteristics	Specified 'weighted' mean nadir Hb concentrations for baseline reporting.
4.3	Mobilization, Transplant, and Conditioning Details	Separated mobilization and conditioning requirements by indication.
4.3	Mobilization, Transplant, and Conditioning Details	Added reporting for total blood volume processed during apheresis (ml).
4.3	Mobilization, Transplant, and Conditioning Details	For dosing details, added incidence of use of back-up cells for subjects with neutrophil engraftment failure
4.3	Mobilization, Transplant, and Conditioning Details	Moved ANC failure criteria to Section 4.4.1 (Adverse Events)
4.3	Mobilization, Transplant, and Conditioning Details	Added reporting and definition of time to platelet recovery.
4.3	Mobilization, Transplant, and Conditioning Details	Added timing of weight measurement to be used in reporting busulfan use in mg/kg.
4.3	Mobilization, Transplant, and Conditioning Details	Added busulfan reporting in AUC (µM*min) as well
4.4 – 4.6	Safety Analyses, Efficacy Analyses, Pharmacodynamic Analyses	Changed ordering of sections to more accurately reflect the protocol: Safety (4.4), Efficacy (4.5), Pharmacodynamics (4.6).
4.4	Safety Analysis	Changed population from ITT to TP population on rates of failure to engraft, rates of infection, and rates of SAEs of transplant procedure or preparation of procedure.
4.4.1	Adverse Events	Added language to indicate that some AEs reported to the Investigations SOC will be recoded to their synonyms under Blood and Lymphatic System Disorders
4.4.1	Adverse Events	Removed absolute days for conditioning and ANC engraftment (Day -8 and 43 respectively). Now based on individual subject timing.
4.4.1	Adverse Events	Modified time-period reporting to be consistent with other Lenti-G studies.
4.4.1	Adverse Events	Added event classifications used to define 'related' events ('Possibly Related' or 'Related')
4.4.1	Adverse Events	Removed category of events reported at each reporting period but added text for an AE table footnote to describe degree of reporting in the study by type of event.
4.4.1	Adverse Events	Added and defined "study procedure related adverse events" as a category of events to be summarized.
4.4.1	Adverse Events	Added and defined "malignancy" as a category of events to be summarized.

Section Number	Section	Changes from Prior SAP Version
4.4.1	Adverse Events	Modified listing of subjects withdrawing due to adverse events, now not limited to prior to drug product infusion.
4.4.1	Adverse Events	Added listing of subjects with malignancies.
4.4.1	Adverse Events	Defined engraftment failure as failure to meet ANC criteria by Day 43.
4.4.1	Adverse Events	Moved platelet engraftment, now reported in Section 4.3.
4.4.1	Adverse Events	Added text for a footnote for AE summaries to indicate collection periods
4.4.2	Laboratory Data	Removed time periods as covered in an earlier section.
4.4.2	Laboratory Data	Additional Clinical laboratory parameters to be evaluated were added – Erythropoietin, Prothrombin Time, and PTT
4.4.2	Laboratory Data	Additional parameters were added for CTCAE shift tables – AP, Calcium. Phosphorous and Potassium
4.4.2	Laboratory Data	A table added to indicate the direction of shift considered for CTCAE shift tables
4.4.3	Transplant-Related Mortality	Removed KM analysis and summarization (any subjects meeting criteria to be reported in a listing).
4.4.4	Vital Signs, Karnofsky Performance Status, and Physical Examination	Removed summaries of Karnofsky data; data will be reported in a listing
4.4.4	Vital Signs, Karnofsky Performance Status, and Physical Examination	For Karnofsky score analysis, added that used for subjects ≥16 years.
4.4.5	Concomitant Medication and Procedures	Removed summaries; data will be reported in a listing
4.4.5	Concomitant Medication and Procedures	Change time periods for reporting (to match AE periods)
4.4.6	Overall survival	Removed summaries; data will be reported in a listing
4.4.6	Overall survival	Limited reporting to TP from study Day 1.
4.4.7	Integration Site Analysis	Retitled section to “Integration site analysis (ISA)” and changed reporting to listings only. New section combines two endpoints from Version 1.0 SAP.
4.4.7	Integration Site Analysis	Removed specific information to be reported in listing (‘number of unique mappable integration sites’).
4.4.8	Replication Competent Lentivirus	Retitled section and changed reporting to listings only.
4.4.8	Replication Competent Lentivirus	Updated information to be reported in listings.
4.5	Efficacy Evaluation	Changed the order of the subsections.
4.5	Efficacy Evaluation	Removed summary reporting with point estimates and 2-sided 90% confidence intervals.

Section Number	Section	Changes from Prior SAP Version
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Added reporting (listings) by indication.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Added that measurements will be 'annualized'.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Added 'Day 182' (Month 6) as relative start point for post infusion reporting, and corresponding changes in text to align with this modification.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Replaced endpoint of reporting from 'Month 18 (or later as applicable' to 'last visit'.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Added secondary analysis for post-treatment reporting: if there is a period of more than 60 days without transfusion, all Hb records between Day 61 and up to the day before next transfusion (inclusive) will also be included. Specified that the lowest value will be selected if multiple Hb records occur on the same day.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Moved reporting when there is a missing Hb value to this section from Section 3.9.
4.5.1	Red Blood Cell Transfusion Requirements and Transfusion Reduction (subjects with TDT or SCD)	Added paragraph for weighted average Hb nadir reporting and comparison to baseline.
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Retitled section to 'Characterization of Transfusion Independence'
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Removed statement that a transfusion of RBCs for a single acute event would not be counted towards the definition of TI.
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Removed summary of proportion of subjects meeting TI.
4.5.2	Characterization of Transfusion Independence (subjects with TDT only)	Removed reporting of transfusion-free survival.
4.5.3	[redacted]	CCI [redacted].
4.5.4	Sickle Cell Disease Related Parameters (subjects with SCD only)	Added paragraph on reporting of hospitalizations due to SCD-related events.
4.5.5	CCI [redacted]	[redacted]

Section Number	Section	Changes from Prior SAP Version
4.5.5	CCI [redacted]	[redacted]
4.5.6	CCI [redacted]	[redacted]
4.5.6	CCI [redacted]	[redacted]
4.5.7	CCI [redacted]	[redacted]
4.5.7	CCI [redacted]	[redacted]
4.5.8	Other Clinical Measures (subjects with TDT or SCD)	Added listing reporting change from baseline in PFT measures for SCD subjects.
4.5.8	Other Clinical Measures (subjects with TDT or SCD)	Oxygen Saturation was added as an additional PFT parameter
4.5.8	Other Clinical Measures (subjects with TDT or SCD)	Removed that echocardiology results at unscheduled visits will be presented in the listing.
4.6	Pharmacokinetic and Pharmacodynamic Evaluations	Added reporting for SEP population, and reporting by indication.
4.6	Pharmacokinetic and Pharmacodynamic Evaluations	Added calculations for each Hb fraction and details for the algorithm when more than one evaluation in the visit window.
4.6	Pharmacokinetic and Pharmacodynamic Evaluations	For VCN, added 'average by subject and by lot' reporting.

Changes between Protocol Defined Analysis and SAP Version 1.0:

There will be an interim analysis for an MAA submission specifically for the indication of TDT, in which no SCD analyses will be performed. Data from this interim analysis for 205 TDT subjects will be reported in an interim CSR. There will be a second interim analysis for this MAA using a later data-cut in which safety data only from all subjects in Study HGB-205 (TDT + SCD) will be pooled with that of other TDT and SCD subjects from other clinical studies in an integrated summary of safety.

Protocol Section	Section Title	Text in Protocol	Change from Protocol in SAP and Rationale

Protocol Section	Section Title	Text in Protocol	Change from Protocol in SAP and Rationale
2.2.2	Efficacy Endpoints	For all subjects: • RBC transfusion requirements (measured in milliliters [mL] per kilogram [kg]) per month and per year post-transplant. • Number of total in-patient hospitalization days (post-transplant discharge) at 6, 12, and 24 months. For severe SCD subjects only: • Number of VOC or acute chest syndrome events at 6, 12, and 24 months. • Evaluation of changes in the nature or frequency of the subject-specific main inclusion criteria.	For TDT subjects only additions include: Clarification of transfusion requirements in the SAP including the following (where post-treatment is measured from 6 months post drug product infusion) % reduction, frequency of pRBC transfusions, average annual pRBC transfusion volume, Weighted average nadir Hb Note: the number of total in-patient hospitalization days has been modified in the current SAP to be post-transplant discharge to last visit. Note: % reduction in the SAP is also categorized into the following categories: ≥ 50%, 60%, 75%, 90% or 100% in average annual pRBC transfusion volume. The clarification above and additional endpoints below for TDT subjects were added for consistency of evaluation across multiple studies using LentiGlobin BB305 to treat TDT, and to support marketing authorization. The endpoints pertained to the following areas: Characterization of Transfusion Independence Iron burden Iron chelation and phlebotomy For SCD subjects only changes include: Further specification of SCD events to include strokes and transient ischemic attacks.
2.2.1	Safety Endpoints	Monitoring of laboratory parameters and frequency and severity of clinical AEs.	"Monitoring of" is changed to "Changes in". Integration site analysis (ISA) is added to clarify that this analysis will be done to allow evaluation of clonal dominance (another endpoint). Added transplant-related mortality assessment at Day 365 as well as 100 days post treatment.

Protocol Section	Section Title	Text in Protocol	Change from Protocol in SAP and Rationale
7.2	Populations for Analysis	The primary population for analysis of both efficacy and safety will consist of those subjects who initiate any study procedures, beginning with mobilization (subjects with β-Thal$_M$) or anesthesia for bone marrow harvest (subjects with SCD); this population will be denoted as the intent-to-treat (ITT) population. All subjects must have at least 2 years of follow-up at a specialized center, in order to be used as their own control for key measurements of clinical events and transfusion requirements. Additionally, analysis will be performed on those who undergo the gene therapy transplantation; should this be a smaller number of subjects, this population will be denoted as the transplant population (TP). …an evaluable population will be defined as those subjects who successfully engraft and have sufficient study visit compliance to acquire primary efficacy data through 24 months post-treatment. Subjects in this population must be compliant with the visit window for the Month 24 evaluations.	The ITT population is defined as the primary population for safety analysis, and TP is the primary population for the analysis of transplant-related safety parameters and efficacy parameters. Successful Engraftment Population (SEP) is defined as all subjects who have successful neutrophil engraftment after drug product infusion. Definitions were added for consistency of populations across multiple studies using LentiGlobin BB305 to treat TDT, and to support marketing authorization
7.3	Procedures for Handling Missing, Unused, and Spurious Data	No imputation will be performed for missing data elements. Subjects in the ITT or TP analysis groups will be considered treatment failures in the primary analysis of stabilization, if they have less than 24 months post-transplant follow-up.	Details of missing data handling rules are added, e.g. rules needed for analysis of safety and efficacy endpoints.
7.4.1	General Methods	Two-sided 90% confidence intervals will be calculated as appropriate.	No confidence intervals will be calculated given the limited sample size (7 subjects, 4 TDT subjects)

Protocol Section	Section Title	Text in Protocol	Change from Protocol in SAP and Rationale
		For disease-specific biological parameters and clinical events, including RBC transfusion requirements and number of total hospitalization days at 6, 12, and 24 months, baseline will be defined as the average of these parameters over the 2 years prior to study entry. For other change from baseline analyses, baseline will be defined as the value closest to, but prior to transplant.	Added additional specification to baseline definitions. Other efficacy and pharmacodynamic parameters, most recent measure prior to conditioning. For safety including key laboratory (hematology and chemistry) parameters, the most recent value prior to mobilization (subjects with TDT) or bone marrow harvest (subjects with SCD). Changes were made to provide most clinically relevant baseline.
7.4.2	Disposition of Subjects	The number of subjects completing the study through 2 years post-transplant and reasons for study discontinuation will be reported.	"through 2 years post-transplant" is changed to "through Month 18' (interim analysis for TDT subjects) as well as through Month 24 (if data are available). Change made to allow an interim analysis when all subjects have completed at least 18 months of follow-up or discontinued.
7.4.3	Demographic and Baseline Characteristics	The following demographic and baseline characteristic factors will be summarized: age (current and age at diagnosis), country of origin, race and ethnicity, time from diagnosis of β-hemoglobinopathy type to confirmation for inclusion in the study, the presence of any significant co-morbid conditions, and the time from diagnosis of β-hemoglobinopathy type to treatment.	Modifications include: Addition of characteristics (all subjects as well as specific to TDT or SCD indication). Eliminate summary table for interim analysis due to small number of subjects; data will be listed. Changes were made to provide most clinically relevant baseline information.
7.5	Efficacy Analysis	The following parameters will be evaluated using descriptive statistics. *(reference to sections 7.5.1 and 7.5.2 in addition to the text below).*	Efficacy reporting to be limited to data listings. Change made given small number of subjects in HGB-205 (overall and by indication)
7.5.2	For SCD Subjects	The number of VOC or acute chest syndrome events at 6, 12, and 24 months	Added additional event types Significant Cerebral Abnormality, Stroke, and TIA, Osteonecrosis, and presence of sickle cell cardiomyopathy.

Protocol Section	Section Title	Text in Protocol	Change from Protocol in SAP and Rationale
7.6	Safety Analysis	AEs will be summarized for those events that occur 1) after signing the informed consent and prior to conditioning; 2) from the start of conditioning until Day 1 (immediately before the start of LentiGlobin BB305 Drug Product infusion); 3) from the start of LentiGlobin BB305 Drug Product infusion on Day 1 through 42 days post-infusion;	Adverse Events: Incidence of AEs will be summarized as follows to align periods analyzed with those of the MAA: After signing the ICF and prior to mobilization Start of mobilization until start of conditioning Start of conditioning until date prior to ANC engraftment Date of ANC engraftment through Month 24 visit. Day 1 through the Month 24 Visit Added categories for summarizing AEs related to study procedures, mobilization/apheresis, and conditioning Added summarization of Malignancies (based on MedDRA SMQ categories)
7.6	Safety Analysis	Laboratory measures will be compared with their corresponding normal ranges and the incidence of abnormal laboratory values will be calculated for each relevant protocol-specified laboratory test	Defined abnormal laboratory reporting Added specific reporting summaries for lab parameters (shift tables using CTCAE version 4.03 criteria), subset listings of ≥ Grade 3 events figures for selected parameters.
7.6	Safety Analysis	Replication-competent lentivirus (RCL) testing will be performed and any positive results will be confirmed	Detailed RCL information to be reported in separate section.
7.6	Safety Analysis	Banked leukocytes will be assayed for insertional mutagenesis by LAM-PCR and sequencing in the event that a malignancy is observed.	Expanded section on ISA reporting
	Additional Information (not defined in Section 7 of protocol)		Addition of section for reporting mobilization, conditioning, and transplant details.
			Added section on transplant related mortality reporting
			Added section on vital sign, Karnofsky performance status, and physical examination reporting.
			Added section on concomitant medications and procedure reporting.
			Added section on overall survival reporting.

6. CLINICAL STUDY REPORT APPENDICES

A list of statistical tables, figures, and data listings, along with a complete set of reporting shells, will be provided in a separate document.

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