STATISTICAL ANALYSIS PLAN

A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia 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-212

Protocol Number:	HGB-212
Protocol Version and Date:	Version 6.0: 10 June 2021
Name of Test Drug:	LentiGlobin BB305 Drug Product (betibeglogene autotemcel)
Phase:	Phase 3
Methodology:	Single Arm, Efficacy and Safety
Sponsor:	bluebird bio, Inc. 455 Grand Union Boulevard Somerville, MA 02145 USA
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Analysis Plan Date:	28 October 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 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

Sponsor: bluebird bio, Inc.

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Sponsor 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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BFU-E	Burst-forming units-erythroid
BMT	Bone marrow transplantation
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
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 Transplant
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
HbF	Hemoglobin F
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant(ation)
ICF	Informed consent form
IRT	Item response theory
ISA	Integration site analysis
ITT	Intent-to-treat

Abbreviation	Definition
IV	Intravenous
KM	Kaplan-Meier
LIC	Liver iron concentration
%LVV+ cells	Percentage of cells containing lentiviral vector sequences
MCH	Mean corpuscular hemoglobin
MCS	Mental component summary
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MOI	Multiplicity of infection
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OS	Overall survival
PCS	Physical component summary
PBLs	Peripheral Blood Leukocytes
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-212, "A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia (TDT) 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 trial.

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.

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 have a β^0/β^0, β^0/IVS-I-110, or IVS-I-110/IVS-I-110 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 have a β^0/β^0, β^0/IVS-I-110, or IVS-I-110/IVS-I-110 genotype at the *HBB* gene

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a single-arm, multisite, single-dose, Phase 3 study with approximately 18 subjects with TDT who have a β^0 or IVS-I-110 mutation at each allele of the *HBB* gene (i.e., β^0/β^0, β^0/IVS-I-110, or IVS-I-110/IVS-I-110 genotypes). Similar to β^0 alleles, the β^+ allele IVS-I-110 is widely recognized as producing little to no β-globin, thus subjects with β^0/IVS-I-110 or IVS-I-110/IVS-I-110 genotypes were grouped with the β^0/β^0 subjects in this study. [redacted]

Subjects 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 subjects.

The study will evaluate the efficacy and safety of autologous hematopoietic stem cell (HSC) transplantation (HSCT) using LentiGlobin BB305 Drug Product, an autologous CD34+ cell-enriched population that contains cells transduced with BB305 lentiviral vector encoding the β^{A-T87Q}-globin gene, suspended in cryopreservation solution. Subjects ≥12 and ≤50 years of age must have TDT with a history of transfusion of at least 100 mL/kg/year of packed red blood cells (pRBCs) in the 2 years preceding enrollment or be managed under standard thalassemia guidelines with ≥8 transfusions of pRBCs per year in the 2 years preceding enrollment. Subjects <12 years of age must have a history of transfusion of at least 100 mL/kg/year of pRBCs in the 2 years preceding enrollment. In addition to having a history of transfusion of at least 100 mL/kg/year of pRBCs in the 2 years preceding enrollment, subjects <5 years of age must 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.

Before treating subjects <12 years of age, the independent Data Monitoring Committee (DMC) will review safety data available from Study HGB-207 and determine whether the study can safely proceed with the treatment of subjects ≥5 and <12 years of age. After [redacted] ≥5 and <12 years of age have attained neutrophil engraftment after LentiGlobin BB305 Drug Product infusion in Study HGB-207 and/or HGB-212, 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 requirement for surgery). It is recommended that subjects should receive pRBC transfusions for any Hb <7 g/dL, and for clinically symptomatic anemia, irrespective of Hb level.

Subjects will be followed in this Protocol for a period of 24 months after LentiGlobin BB305 Drug Product infusion. Thereafter subjects will be asked to enroll in a separate long-term follow-up Protocol (LTF-303) 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 Parameters

1.2.6.1. Efficacy Endpoints

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 transfusion independence (TI)
  - Proportion of subjects who meet the definition of TI at Month 24 Visit
  - Duration of TI
  - Time from drug product infusion to achievement of TI
  - Weighted average Hb during TI
- Characterization of transfusion reduction (TR)
  - The proportion of subjects who meet the definition of "transfusion reduction" (TR), defined as demonstration of a ≥60% reduction in the annualized volume of pRBC transfusion requirements (in mL/kg) in the post-treatment time period from 12 months post-drug product infusion through Month 24 (approximately a 12-month period), compared to the annualized mL/kg pRBC transfusion requirement during the 2 years prior to study enrollment
  - Proportion of subjects with 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 the Month 24 Visit

- 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
- 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 at 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 Visits
  - Change in cardiac T2* on MRI at baseline to Month 12 and Month 24 Visits
  - Change in serum ferritin at baseline to Month 12 and Month 24 Visits
- 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 comparing annualized number of pRBC transfusions, number of hospitalizations, and number of days hospitalized from

12 months post-drug product infusion through the Month 24 Visit with 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-globins, 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 from 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 Endpoints:

- 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 neutrophil engraftment (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-related 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 very unlikely to happen spontaneously in patients with TDT. 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 transfusion independent on the study would represent a clinically meaningful treatment effect, to be assessed against the morbidity of the procedure.

Approximately [redacted] will be treated with drug product; at least [redacted] must be without an IVS-I-110 mutation and at least [redacted] must be <18 years of age. Replacement subjects may be added if subjects are screen failures or withdraw prior to drug product infusion.

The proposed sample size 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 have become TI). Among the proposed sample size of 18 treated subjects, a success criterion of 55.6% (10 out of 18 subjects) is proposed, which would yield a lower 1-sided 97.5% exact confidence bound of 30.8%, exceeding the 30% minimal criterion.

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 characteristics, 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 (CIs), as appropriate, will be presented on selected parameters, as described in the sections below. The exact CI for proportions will be calculated using the Clopper-Pearson 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 Global B3 format (March 2021 or later).

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, and in-patient hospitalizations (number and duration). For these parameters, where applicable, 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 screening, 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 shift tables 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 the 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 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 age, race, sex and genotype (β^0/β^0 vs. non-β^0/β^0) as well as TI status on selected tables. Age will be stratified based on age at informed consent/assent >=18, <18, <18 and >=12, <12, and >=12 years. Further stratification on <12 years may also be employed if sufficient number of subjects were enrolled in each category: <6, 6 to <12 years. Disposition status will also be summarized by investigational site, with investigational site defined as the site where the subject was consented. Additionally, Mobilization/Apheresis details will be summarized overall and according to splenectomy status at baseline.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects withdrawn from the study prior to drug product infusion will be replaced.

Subjects who enroll in the trial but discontinue prior to myeloablation 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. In the rare case a subject undergoes myeloablation but does not undergo LentiGlobin BB305 Drug Product infusion or undergoes drug product infusion with no evidence of engraftment and receives back-up cells, follow-up should continue on trial for at least 3 months, or until resolution of any study-procedure related AEs, whichever is later.

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 and the number of pRBC volume 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 300 mL/unit will be used. If the volume is unknown or unit is missing, for transfusions rendered before study drug infusion, the mean volume that the subject has received in the 2 years prior to study enrollment will be imputed. If the transfusion is after the study drug infusion, then the imputed volume will be the mean volume that subject 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.

3.10.2. Partial Dates

When tabulating AE data, partial onset dates will be handled as follows. The partial end date of AE will be imputed before the start date is being imputed. For AE end dates, an event missing the day of the month will be set to the last day of the month or the last follow-up date, whichever occurs first; if both the day and 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 drug product infusion and the event stop date is equal to or after the date of 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 drug product infusion. 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 treatment and the event stop date is equal to or after the date of drug infusion. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A complete missing onset date will be coded as the day of drug product infusion or AE stop date, whichever is earlier.

Partial dates for concomitant medications and iron removal therapy will be handled as follows:

The partial end date of concomitant medication will be imputed before the start date is being imputed. If the day of the month is missing, the end date will be set to the last day of the month or the last follow-up date, whichever occurs first. If the month and day is missing, the end date will be set to December 31 or the last follow-up date, whichever occurs first. If the end date is completely missing, it will set to the last follow-up date except for iron removal therapy, in which case it will not be imputed. For partial start date, if the day of the month is missing, it will be set to the first day of the month. If the start day and month are both missing, the day and month will be set to January 1. A complete missing start date will be set to the day before the informed consent date. In any case, if the imputed start date is after end date, it will be set to the end date.

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 an earlier date of diagnosis 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 the 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 t0 up to the latest observed Hb is ≥9 g/dL, 2) the subject has at least 6 months of observed Hb from t0 to last follow-up, and 3) the subject has remained off pRBC transfusions from t0 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 t0 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.

To minimize bias that may be introduced by imputation, missing information of endpoints other than TI unless related to the characterization of TI 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, 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 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 are listed in Table 1.

Table 1: Midpoint Windows for Hematology

Time point		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 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 fraction data are listed in Table 3.

Table 3: Midpoint Windows for VCN and Fraction Data

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 study 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 Immunology Assessment and RCL are listed in Table 5.

Table 5: Midpoint Windows for Immunology Assessment 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 neutrophil engraftment (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 in each analysis will take into account input from regulatory agencies and applicable regulatory guidance.

3.14. 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.

3.15. Final Analyses

A final analysis will be performed when all subjects treated with LentiGlobin BB305 Drug Product complete the study. The end of Study HGB-212 is defined as the last visit for the last subject.

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.

4.2. Demographics and Baseline Characteristics

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

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, and number of in-patient hospitalizations and duration of hospitalization) will also be summarized. The mean pRBC volume (mL/kg/year) as well as the mean number of pRBC transfusions/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.

Summary tabulations will be produced for the ITT population, TP and SEP if they differ; all demographic and baseline data will be included in data listings.

4.3. Mobilization, Transplant and Conditioning Details

Information to be tabulated for mobilization cycles includes:

- Number of mobilization cycles/subject
- 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 for each cycle (mL/cycle)
- Average total blood volume processed during apheresis across all cycles (mL/cycle) (for subjects with multiple cycles, total blood volume will be average across cycles)

- Number of CD34+ cell count collected (cells $\times 10^6$/kg)
- Number of CD34+ cells sent for transduction (cells $\times 10^6$/kg)
- Number of CD34+ cells sent for rescue (cells $\times 10^6$/kg)

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

Drug product dosing and infusion 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 1 drug product lot, $\times 10^6$/kg)
- VCN of drug product (DP VCN; weighted average per subject if more than 1 drug product lot, and average per lot; vector copies per diploid genome, 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 1 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 $\geq 0.5\times 10^9$/L after a post-drug product infusion 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 is considered to be $<0.5\times 10^9$/L for the purposes of calculating day of neutrophil recovery.
- Day of platelet engraftment (PE) (defined as the day on which the first of 3 consecutive unsupported platelet counts of $\geq 20\times 10^9$/L obtained on different days starting after platelet counts dropped to $<20\times 10^9$/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 $< 20 \times 10^9$/L, the initial post-infusion nadir may be used as a post-transplant value of $< 20 \times 10^9$/L based on clinical judgement.); to be summarized as a continuous measure as well as categorized into ≤30 days, >30 to ≤60 days, >60 days to ≤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 DP infusion (months)

If a subject had multiple lots of drug product, the DP VCN, %LVV+ 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 (any prophylactic and empiric anti-convulsive, antifungal, and antibiotic treatments, and other supportive care usage for the preparative regimen) will be included in the concomitant medications 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. The volume of each type of blood product transfusion (mL/kg) will also be reported. 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 the primary analysis set for all efficacy analysis. Sensitivity analysis will be performed on the SEP if SEP differs from the TP for the primary efficacy endpoint.

4.4.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who meet 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. The calculation of transfusion independence (TI) is defined as follows:

- Calculation of time period of TI will start when the subject achieves a 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, 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, or until next 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. 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. For interim analysis, the proportion will be calculated based on the number of subjects who are TI evaluable. After drug product infusion, a subject is evaluable for "TI at any time" if they have already satisfied the TI criteria at any time, or if they completed the Month 24 Visit, or if they will not reach TI in the study based on the following 2 criteria: (1) if the subject is receiving chronic transfusions after 324 days (750 days – 14 × 30.4375 days) of follow-up, or (2) if the subject's Hb level never reaches t0 (Hb ≥9 g/dL with no transfusions in the preceding 60 days) by 385 days (750 days – 365.25 days) of follow-up.

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.

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. Analyses of Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be descriptively analyzed.

Characterization of subjects achieving transfusion independence (TI):

- Proportion of subjects who meet the definition of TI at the Month 24 Visit
- Duration of TI
- Time from drug product infusion to achievement of TI
- Weighted average Hb during TI

The above parameters will be displayed in summary tables using descriptive statistics.

The duration of TI will be calculated for TI subjects only. It will be analyzed using Kaplan-Meier (KM) time to event summary statistics, including the median, 25th and 75th percentiles and 2-sided 95% CIs. 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. Imputation on missing Hb assessments due to COVID-19 and the primary and sensitivity analysis on weighted average Hb during TI will be performed as described in Section 3.10.3.

Characterization of transfusion reduction (TR) (overall and by subject):

- Proportion of subjects who meet the definition of TR, defined as demonstration of a ≥60% reduction in the annualized volume of pRBC transfusion requirements (in mL/kg) in the post-treatment time period from 12 months post-drug product infusion through Month 24 (approximately a 12-month period), compared to the annualized mL/kg pRBC transfusion requirement during the 2 years prior to study enrollment.
- Proportion of subjects with a reduction in the mL/kg/year 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. These categories will be analyzed as point-estimates of the proportion of subjects meeting the respective definitions; the 2-sided 95% confidence interval will be included.
- Annualized number of pRBC transfusions from 12 months post-drug product infusion (Day 365) through the Month 24 Visit compared to the annualized number of transfusions during the 2 years prior to enrollment.
- Annualized volume of pRBC transfusions (mL/kg) from 12 months post-drug product infusion (Day 365) through the Month 24 Visit compared to the annualized volume of transfusions (mL/kg) during the 2 years prior to enrollment.

Below TR parameters will be presented in summary tables using descriptive statistics:

- Time from drug product infusion to last pRBC transfusion. If no post-drug product infusion pRBC transfusion then time will be considered 0.
- Time from last pRBC transfusion to the Month 24 Visit. For interim analysis, the last follow-up will be used if the Month 24 Visit has not yet been reached.

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 of percent reduction in transfusion requirements. The point-estimate of the proportion of subjects achieving at least 50%, 60%, 75%, 90% or 100% TR, with a 2-sided 95% CIs will be reported. The 95% CIs will be derived using the Clopper-Pearson exact binomial method. Any change in transfusion requirements will be determined by comparing the percent difference in mL/kg/year of 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. For interim analysis, the last follow-up will be used if the Month 24 Visit has not yet been reached.

The weight at or closest to the date of transfusion will be used in calculations of pRBC transfusion requirements. pRBC transfusions due to an acute event will not be included. A sensitivity analysis will be conducted for transfusion requirement analyses utilizing the time period of 6 months post-drug product infusion (Day 183) through the Month 24 Visit.

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

Time from drug product infusion to last pRBC transfusion and time from last pRBC transfusion to the Month 24 Visit 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. In 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.

For any interim analysis, transfusion requirement endpoints utilizing the 12 months post-infusion to the Month 24 Visit period may be modified to the period post-hospital discharge through last follow-up to detect any emerging trends in the transfusion requirement data. An additional sensitivity analysis will be performed on subjects who complete Month 18 Visit as appropriate.

The following additional sensitivity analyses may be performed for baseline transfusion requirements

a. 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)

Transfusion reduction-related parameters may also be summarized by TI status.

- 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

The 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 61 days after the last pRBC transfusion 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.

- Unsupported total Hb levels over time including Month 6, Month 9, Month 12, Month 18, and Month 24 following drug product infusion. Unsupported total Hb levels are defined as the scheduled 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, age group, genotype and for overall TP.
- The proportion of subjects with unsupported total Hb levels ≥10 g/dL, ≥11 g/dL, ≥12 g/dL, ≥13 g/dL, ≥14 g/dL at Month 6, Month 9, Month 12, Month 18, and Month 24 following drug product infusion. Subjects with unsupported total Hb levels meeting the thresholds will be summarized overtime. This analysis will be presented by sex, age group, genotype and for 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 after 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 after drug product infusion
- Evaluation of the change in iron burden over time, as measured by:
  - Change in LIC by MRI (mg/g) from baseline to Month 12 and Month 24 Visits
  - Change in cardiac T2* on MRI from baseline to Month 12 and Month 24 Visits
  - Change in serum ferritin from baseline to Month 12 and Month 24 Visits. Summary statistics for additional visits per study Protocol SOE will also be provided.

The number and percentages 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 presented as both raw and percentage change from baseline and presented in by-subject listings, as well as summarized using descriptive statistics grouped by TI status. LIC, cardiac T2*, and serum ferritin data will be presented graphically over time by-subject and over time in box-plot by TI status as applicable.

Quality of life (QoL) assessments are collected at Screening, Month 3 (for EQ-5D and FACT-BMT only), 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

The following assessment of HRQoL will be included:

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. 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 with pediatric and adult results presented separately. 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 (BMT). It consists of the general Functional Assessment of Cancer Therapy (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, along with the change from baseline. FACT-BMT information by subject will be provided in data listings.

4.4.3. Analyses of Exploratory Efficacy Endpoints

- Measures of health resource utilization (including comparing annualized number of transfusions, number of hospitalizations, and number of days hospitalized, from 12 months post-drug product infusion through Month 24 Visit, with 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.)
- Length of in-patient hospital stay from initiation of conditioning to discharge

- 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: reticulocytes, nucleated RBC (erythroblast), 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 (in particular: proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, orthochromatic erythroblasts), 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 and 3 to 4 will be summarized. In addition, selected parameters will be presented graphically over time by-subject and over time in box-plot by TI status as applicable. 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.

4.4.4. Analyses of Other Clinical Measures

The following data will be listed:

- Pulmonary function testing (PFT) (including % oxygen saturation as measured by pulse oximetry, Dlco; % predicted Dlco,), and PFT interpretation at all visits. If subject cannot perform spirometry or lung diffusion capacity test due to age or cognition-related restrictions, then respiratory exam, chest radiograph, and pulse oximetry will substitute for these assessments.
- 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 from TP) and will include summary tables with descriptive statistics, summary figures (all subjects, all values versus time on the x-axis), displaying the items below:

- Peripheral blood VCN post-drug product infusion over time (tabulated, and all subjects in one figure) and correlation of peripheral blood VCN at early time points post-drug product infusion to selected drug product characteristics.
- The ratio of α-globin to all β-like-globin-chains (i.e., all β [including β^{A}, and $\beta^{A\text{-}T87Q}$], γ, and δ chains), tabulated overall and by subject.

- 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, selected drug product characteristics, as well as clinical outcomes.
- Hb fractions over time (including HbA^{T87Q}, HbA, HbA_2, and HbF, as relevant, calculated using ratio data and total Hb), by-subject (g/dL) and overall summaries by timepoint. By-subject figures will be provided for HbA^{T87Q}. By-subject figures with all fractions for a given subject in one plot will also be prepared, which will include pRBC transfusions indicated by vertical lines on these plots. 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 = β^{A}-Globin to All β-Like-Globin-Chains*total Hb
  - HbA_2 = δ-Globin to All β-Like-Globin-Chains*total Hb
  - HbF = (γ^{G}-Globin to All β-Like-Globin-Chains+γ^{A}-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, 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). Within a given midpoint window for a particular subject, if there are multiple fraction results, an average will be calculated and used in summary tables and figures.

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 may 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 also be performed in the TP on rates of failure to engraft and rates of AEs by system organ class (SOC) and preferred term (PT). Treatment Emergent Adverse Events (TEAEs) will be defined as those occurring during or after drug product Infusion.

Given the nature of the different interventions before drug product infusion, the safety data will also be described in relation to the occurrence during the following periods: ICF signature prior to the beginning of mobilization (ICF to <M), mobilization/apheresis to prior to the beginning of the myeloablative conditioning (M to <C); from the beginning of conditioning to prior to

neutrophil engraftment (C to <NE) and from neutrophil engraftment to Month 24 visit (NE to M24). As mentioned in the paragraph above, events occurring during or after drug product infusion through the last study visit (D1 to M24) will be considered TEAEs.

4.6.1. Adverse Events

All AEs will be collected from informed consent through the Month 24 Visit for all subjects who undergo study procedures (i.e., all subjects except for screen failures).

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using SOC and PT. The AE Grade will be based on the 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 TEAEs by SOC and preferred term. All AEs will be assessed in terms of their seriousness, severity, outcome and relationship to LentiGlobin BB305 Drug Product. 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. AEs will be summarized for those events that occur in the intervals mentioned in Section 3.12 . For TEAEs 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 ICF to M24 by selected subgroups (sex, age at informed consent, race, genotype) (Period from ICF to Month 24 and Day 1 to Month 24 Visit only)
- Incidence of all AEs by maximum severity (summarized for the worst grade in each period based on the AE start date of all reported events)
- Incidence of all Treatment Emergent AEs by maximum severity*
- Incidence of all AEs related to Plerixafor by maximum severity**
- Incidence of acute and/or chronic GVHD*
- AEs attributed to Mobilization/Apheresis**
- AEs attributed to Conditioning**
- SAEs attributed to Conditioning**

* TEAEs only.
** Based on investigator attribution on CRF for events not related to study drug.

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, AEs related to drug product and treatment-emergent events of interest.

Events Attributed to Mobilization/Apheresis

AEs designated on the CRF as related 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.

Potential Hy's Law

Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2x ULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality will be summarized.

Engraftment

The incidence and timing of NE and PE will be calculated and tabulated.

Events 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*	Serum transferrin receptor*
Reticulocyte/Erythrocyte*	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	Lactic 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 and 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 may be derived as needed.

Additional exploratory clinical laboratory tests include hormonal levels and immunological cell analyses. Number and percentages 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 criteria. Lab results that meet the potentially clinically significant criteria will be listed and summarized based on study periods in Section 3.12 . The potentially clinically significant thresholds used are listed in the following 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	≥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	≤75 $\times 10^9$/L	≥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 12, Month 12 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 (ALP)	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 over time by-subject and over time in box-plot by TI status as applicable.

In addition, by-subject figures will be provided including a single subject for each parameter for Hb (with pRBC transfusions noted), platelets (with platelet transfusions noted) and absolute reticulocyte (with phlebotomy noted). Also, by-subject figures (all subjects on a single plot) will be provided for neutrophils and platelets over time. For adolescents, hormonal results will be presented in listings.

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 percent of subjects with potentially clinically significant (CS) vital signs parameters on D1 will be presented and will be stratified according to pre or post infusion.

The following criteria will be used to determine potentially CS values:

Variable Name	Potentially CS – Low if: Observed Value is:	AND	Potentially CS – Low if: Decrease from Baseline is:	Potentially CS – High if: Observed Value is:	AND	Potentially CS – High if: 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, along with change scores from baseline.

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

Karnofsky and Lansky performance status will be presented for each subject 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. Results will be assigned an anatomic therapeutic class and preferred name. Medications will be provided in a by-subject listing and according to the intervals mentioned in Section 3.12 . All concomitant treatments/procedures (including transfusions) will also be displayed in a listing. Regarding 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 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.

4.6.7. Integration Site Analysis

An integration site analysis (ISA) will be performed on peripheral blood leukocytes (PBLs) starting at Month 6 after infusion of drug product.

Clonal predominance is defined as:

1. Single IS: any single top 10 IS result >30% of the total IS with a peripheral VCN >0.3 c/dg, and corresponding IS-specific VCN from qPCR >0.5 c/dg
2. Group of IS: for a group of IS with frequencies within 20% of the reference IS, the combined group IS frequencies > 30% with a peripheral VCN >0.3 c/dg, and the IS-specific VCN from qPCR for any IS in the group >0.5 c/dg
3. Any single IS-specific VCN from qPCR is >0.5 c/dg

If criteria for a predominant clone have been met, a new sample is to be collected per Protocol as soon as possible but no later than within 3 months from the identification of the predominant clone, and retrospective testing by IS-specific qPCR is to be performed on samples previously collected as available.

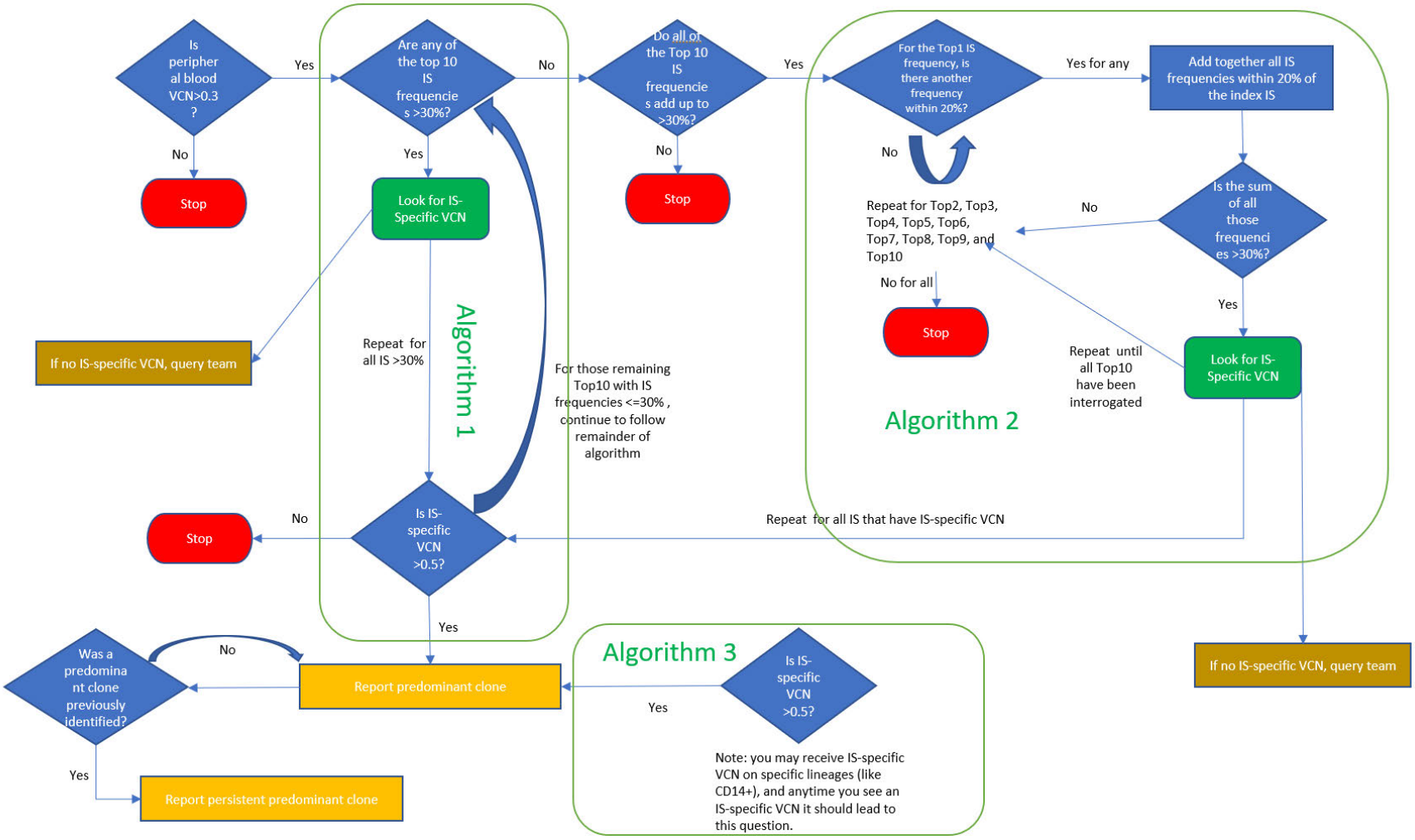
Persistent clonal predominance is defined as:

1. Clonal predominance criteria #1, #2, or #3 above met on a specific gene at least two times anytime during follow-up.

The number and percentage of subjects who meet the ISA clonal predominance and persistent clonal predominance criteria will be summarized. The total number of unique mappable IS in PBLs at each visit, as well as the highest frequency and highest total number of unique mappable IS within subject across all visits, will be summarized. Additional analysis may be performed as appropriate.

The details on clonal predominance and persistent clonal predominance may be found below in Figure 1.

Figure 1: Schematic diagram for assessment of clonal predominance and persistent clonal predominance



CCI [redacted]

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 and not detected, and by co-culture assay as detected or not detected for each visit, as relevant, and summarized.

5. CHANGES TO PLANNED ANALYSIS

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

5.1. Changes from Analyses Specified in Study Protocol

Specified in Protocol	Changes in SAP
	None

5.2. 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	Updated WHO Drug Dictionary version to Global B3 format (March 2021 or later).
3.11	Visit Windows	Removed details of iron study parameters.
3.11	Visit Windows	Added visit windows for ISA.
4.4.3	Analyses 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."
4.6.1	Adverse Events	Removed the listing of recoded PTs
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."

Section Number	Section	Changes
4.6.7	Integration Site Analysis	If criteria for a predominant clone have been met, a new sample is to be collected per protocol as soon as possible but no later than within 3 months from the identification of the predominant clone, and retrospective testing by IS-specific qPCR is to be performed on samples previously collected as available.
4.6.1	Adverse Event	**Potential Hy's Law** Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2x ULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality, must be reported.
4.6.2	Laboratory Data	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 12, Month 12 through Month 24 Visit, Day 1 (date of LentiGlobin BB305 Drug Product infusion) through Month 24 Visit.

6. APPENDIX

Event 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 MedDRA HLT = Autoimmunity analyses, Anaemias hemolytic immune 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. REFERRENCE

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Signature Page for HGB_212_SAP v5.0 v1.0

Approval Task	PPD Clinical Research Development 01-Nov-2022 14:08:13 GMT+0000

Approval Task	PPD Pharmacovigilance/Safety 01-Nov-2022 18:05:05 GMT+0000

Approval Task	PPD Biostatistics 02-Nov-2022 16:39:13 GMT+0000

Approval Task	PPD Regulatory Strategy 03-Nov-2022 01:07:18 GMT+0000

Signature Page for HGB_212_SAP v5.0 v1.0