STATISTICAL ANALYSIS PLAN

The Guard1 Trial, an Open-Label, Multinational Phase 1/2 Study of the Safety and Efficacy of Ex Vivo, Lentiviral Vector-Mediated Gene Therapy AVR-RD-02 for Subjects with Type 1 Gaucher Disease

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SAP APPROVAL

Protocol Title:	The Guard1 Trial, an Open-Label, Multinational Phase 1/2 Study of the Safety and Efficacy of Ex Vivo, Lentiviral Vector-Mediated Gene Therapy AVR-RD-02 for Subjects with Type 1 Gaucher Disease
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Protocol Number:	AVRO-RD-02-201
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Author:

[redacted]
Executive Director, Head of Biostatistics
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Signature: [redacted]

Date: 28-Aug-2023

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted]
Director, Clinical Physician
AVROBIO, Inc.

Signature: [redacted]

Date: 26-Aug-2023

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Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
GCase	β-glucocerebrosidase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutical Chemical (classification)
BMI	Body mass index
BPI-SF	Brief Pain Inventory-Short Form
cDNA	Complementary deoxyribonucleic acid
CRF	Case Report Form
CS	Clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DP	Drug Product
ECG	Electrocardiogram
eCRF	Electronic case report form
ERT	Enzyme replacement therapy
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSC	Human stem cell
ICH	International Conference on Harmonization
IV	Intravenous
LSD	Lysosomal storage disorder
LV	Lentiviral vector
Lyso-Gb1	Glucosylsphingosine
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

Abbreviation	Term
NCS	Not clinically significant
LOCF	Last Observation Carried Forward
OC	Observed Cases
PCS	Physical Component Summary
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
qPCR	Quantitative polymerase chain reaction
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short Form 36
SOC	System Organ Class
SOP	Standard Operating Procedure
VCN	Vector copy number
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

1. INTRODUCTION

AVRO-RD-02-201 is a Phase 1/2 multinational, open-label study to assess the safety and efficacy of AVR-RD-02 in approximately 8 to 16 subjects (male or female) who are ≥18 years and ≤50 years at Screening with a confirmed diagnosis of Type 1 Gaucher disease (based on clinical phenotype and deficient GCase enzyme activity in peripheral blood). The planned study may consist of 2 arms, enrolling switch-stable subjects (who have undergone ERT) and treatment-naïve subjects (who have not undergone ERT or SRT) sequentially.

This statistical analysis plan (SAP) for study AVRO-RD-02-201 is developed based on Amendment 6 of the protocol dated June 15, 2022. The purpose of this SAP is to ensure that the data listings and summary tables which will be produced, and the statistical methodologies that will be used, are comprehensive and appropriate for the analysis of the study objectives specified in the protocol.

Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviation from the final SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) will be documented (and justified) in the clinical study report (CSR). The reason for the changes and the datasets and outputs that are affected will also be documented on a form which is reviewed by the reviewers of this SAP and signed off by the author of the SAP, the Head of Biostatistics (or designated designee) and Clinical Lead.

This SAP supersedes the protocol in all specifications associated with data analyses and statistical methodologies.

The study was prematurely discontinued.

AVROBIO, Inc. will perform all efficacy and safety statistical analyses.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objectives

The primary objectives of this study are to:

- Evaluate the safety and tolerability of AVR-RD-02 investigational product.
- Assess measures of engraftment of gene-augmented HSCs by determining average vector copy number (VCN) in peripheral blood leukocytes (PBLs) and bone marrow stem and progenitor cells using quantitative polymerase chain reaction (qPCR) and/or droplet digital polymerase chain reaction (ddPCR) analysis.
- Evaluate the effect of AVR-RD-02 investigational product on clinical and biomarker indices of Type 1 Gaucher disease, including:
    - Spleen volume
    - Liver volume
    - Hemoglobin concentration
    - Platelet count
    - Glucosylsphingosine (lyso-Gb1) plasma levels.

2.1.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate GCase enzyme activity in peripheral blood (PBLs).
- Evaluate the need for enzyme replacement therapy (ERT) following treatment with AVR-RD-02 investigational product.
- Assess the immunogenicity of AVR-RD-02.
- Evaluate the effect of AVR-RD-02 investigational product on clinical and biomarker indices of Type 1 Gaucher disease, including:
    - Chitotriosidase enzyme activity in plasma.
    - Bone marrow burden (BMB) scoring by bone MRI.
    - Bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA).

2.1.3. Exploratory Objectives

The exploratory objectives are to:

- Evaluate the effect of AVR-RD-02 investigational product on Quality of Life (QoL) assessed by the 36-Item Short Form Health Survey (SF-36)
- Evaluate the effect of AVR-RD-02 investigational product on pain assessed by the Brief Pain Inventory-Short Form (BPI-SF)
- Assess exploratory biomarkers for Gaucher disease in serum, plasma, PBLs, and urine
- Assess the impact of the conditioning regimen on reproductive potential

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoints

Primary efficacy endpoints:

- Change from Baseline in spleen volume assessed by abdominal MRI at Weeks 26, 39, and 52
- Change from Baseline in liver volume assessed by abdominal MRI at Weeks 26, 39, and 52
- Change from Baseline in hemoglobin concentration at Weeks 13, 26, 39, and 52
- Change from Baseline in platelet count at Weeks 13, 26, 39, and 52
- Change from Baseline in lyso-Gb1 plasma levels at Weeks 13, 26, 39, and 52

Primary engraftment endpoint:

- Average VCN assessed by qPCR and/or ddPCR in peripheral blood at Baseline and Weeks 13, 26, 39, and 52 and in bone marrow aspirate at Baseline and Weeks 26 and 52

2.2.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints:

- Change from the Baseline in GCase enzyme activity level in PBLs at Weeks 13, 26, 39, and 52
- ERT frequency and dosing between Weeks 26 and 52, inclusive
- Change from Baseline in anti-GCase total antibodies, and subsequent titers and isotopes at Weeks 5, 13, 26, 39, and 52
- Change from Baseline in BMD assessed by DXA at Week 52
- Change from Baseline in clinical and biomarker indices of Type 1 Gaucher disease, including the following:
  a. Chitotriosidase enzyme activity levels in plasma at Weeks 13, 26, 39, and 52
  b. BMB score as assessed by bone MRI at Weeks 26, 39, and 52

2.2.1.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints:

- Change from Baseline in QoL as assessed by SF-36 at Week 52
- Change from Baseline in pain as assessed by BPI-SF at Weeks 13, 26, 39, and 52
- Change from Baseline in exploratory biomarkers for Gaucher disease in serum, plasma, urine, and whole blood derived leukocytes, or subpopulations at Weeks 13, 26, 39, and 52
- Evaluate exploratory genomic biomarkers for Gaucher disease in whole blood at Screening (ie, CHIT1, gene encoding chitotriosidase)
- Average VCN and ISA results in both whole blood and bone marrow cells at specified time points

2.2.2. Safety Endpoints

2.2.2.1. Primary Safety Endpoints

Primary safety endpoints:

- Incidence and severity of AEs, incidence of serious adverse events (SAEs), and incidence and severity of AEs of interest, including drug-product related AEs, infections, and malignancy
- Change from Baseline in clinical laboratory values relevant to safety
- Change from Baseline in vital signs
- Change from Baseline in ECG findings and Weeks 26 and 52

2.2.2.2. Exploratory Safety Endpoints

Exploratory safety endpoints:

- Change from Baseline in ovarian reserve as assessed by anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (female subjects only) at Weeks 26 and 52
- Change from Baseline in menstrual cycle (female subjects only) monthly through Week 52
- Change from Baseline in sperm count, volume, sperm concentration, total motility, progressive motility, and morphology (male subjects only) at Week 52

2.3. Statistical Hypotheses

No formal hypothesis tests or statistical models are planned.

2.4. Pharmacokinetic (PK) and PK/Pharmacodynamic (PD) Hypotheses

Not applicable for this study.

3. STUDY DESIGN

AVRO-RD-02-201 is a Phase 1/2 multinational, open-label study to assess the safety and efficacy of AVR-RD-02 in approximately 8 to 16 subjects (male or female) who are ≥18 years and ≤50 years at Screening with a confirmed diagnosis of Type 1 Gaucher disease (based on clinical phenotype and deficient GCase enzyme activity in peripheral blood). The planned study may consist of 2 arms, enrolling switch-stable subjects (who have undergone ERT) and treatment-naïve subjects (who have not undergone ERT or SRT) sequentially:

- Switch-stable arm: Subjects who have undergone ERT ≥ 15 U/kg and ≤ 60 U/kg every other week (or equivalent; ie, any combination of infusions resulting in a total monthly ERT dose of > 30 U/kg and < 120 U/kg) for ≥ 24 consecutive months for Gaucher disease at the time of Screening. Switch-stable subjects must discontinue ERT at least 2 weeks before the scheduled transplant day. Switch-stable subjects who have been on ERT and substrate reduction therapy (SRT) must not have received SRT within 12 months of Screening.
- Treatment-naïve arm: Subjects with Type 1 Gaucher disease who have never received either ERT or SRT for Gaucher disease or have not received either ERT or SRT for Gaucher disease within 12 months of Screening (ie, treatment-naïve subjects). Enrollment will follow a similar scheme as for the switch-stable subjects.

Initially, 1 adult, switch-stable subject will undergo treatment with AVR-RD-02. Following Week 5 (Day 30) post-transplant data review by an independent Data Monitoring Committee (DMC), if it is determined that study enrollment may proceed, a second safety cohort 1 adult switch-stable subject may undergo mobilization. If DMC data review of these initial 2 subjects indicates no significant safety concerns, enrollment may be expanded to include unrestricted enrollment of the switch-stable study arm. In addition, the treatment-naïve study arm will be open to enrollment and will follow the same gated enrollment scheme as outlined above for the switch-stable arm. Neither switch-stable subjects nor treatment-naïve subjects will receive ERT following gene therapy, unless clinically warranted by prespecified criteria.

Five study periods (Screening, Baseline, Pre-gene Therapy Infusion, Gene Therapy Infusion, and Post-gene Therapy Infusion Follow-up) comprise the study. During the Screening Period (up to 60 days), written informed consent will be obtained and the subject will complete other Screening procedures to confirm study eligibility. Once study eligibility is confirmed, subjects will enter the Baseline Period (up to 7 days) during which time assessments will be performed to establish pre-gene therapy infusion baseline. Once baseline assessments are complete, the subject will enter the Pre-gene Therapy Infusion Period (approximately 8 weeks to 10 weeks [in some instances, the Pre-gene Therapy Infusion Period may be extended beyond 10 weeks due to subject and/or site availability to initiate conditioning]) during which time mobilization, apheresis, AVR-RD-02 investigational product preparation and testing for release, conditioning regimen administration, and conditioning washout period will take place. Enzyme replacement therapy must be discontinued at least 2 weeks before the scheduled gene therapy infusion day. Following completion of the Pre-gene Therapy Infusion Period, the subject will enter the Gene Therapy Infusion Period (1 day) during which AVR-RD-02 infusion will take place. After AVR-RD-02 gene therapy infusion, the subject will enter the Post-gene Therapy Infusion Follow-up Period (approximately 52 weeks) during which time periodic safety and efficacy assessments will be performed to assess measures of safety, engraftment, and clinical response post-gene therapy infusion. Post-gene therapy infusion follow-up will occur at the following time points: Week 1 (Days 1 through 7), Week 2 (Days 10 and 14), Week 5 (Day 30), Week 9 (Day 60), Week 13 (Day 90), Week 18 (Day 120), Week 22 (Day 150), Week 26 (Day 180), Week 39 (Day 270), and Week 52 (Day 365). Subjects that withdraw any time after gene therapy infusion or complete this study have the opportunity to

participate in the long-term follow-up study. During the Post-gene Therapy Infusion Period, subjects will not receive ERT unless prespecified laboratory and clinical criteria, which suggest the need for ERT initiation, are met.

Visit delays due to the global pandemic (coronavirus disease 2019 [COVID-19]) or other unforeseen reasons may necessitate that some procedures/assessments be performed locally, performed out of window, or repeated if performed outside the acceptable timelines for this study. Under such circumstances and in consultation with the Sponsor, remote visits (eg, telemedicine, home nursing visits, etc.) may be considered and may replace some protocol procedures/assessments, when possible. If required, COVID-19 testing will be performed per the institutional guidelines prior to protocol procedures/assessments. To facilitate detection of AEs, other suitable healthcare providers of study subjects (eg, primary care physician, physician's assistant, nurse practitioner, or equivalent) may be engaged in notifying participating Investigators of AEs being collected for the study. Similarly, blood collection on dried blood spot (DBS) cards for GCase activity measurement may occur at the indicated study time points in mitigation of unforeseen logistic delays.

Individuals may be allowed to re-screen based on discussions with the Principal Investigator (PI) and the Sponsor's medical representative or designee's review and approval. Subjects who discontinue from the study prior to infusion of AVR-RD-02 will be replaced.

An independent DMC will be established for the study to review safety and efficacy information during the Pre-transplant, Transplant, and Post-transplant Follow-up Periods of the study to assess for signals that may preclude continued study enrollment and/or necessitate changes to the protocol.

Details on the DMC including meeting frequency will be outlined in a DMC Charter for the study.

The DMC will review data from the safety and efficacy assessments periodically throughout the study to ensure the ongoing safety of subjects.

Final statistical analysis for the study will be performed after all enrolled subjects complete the Week 52 assessments (or prematurely discontinue the study).

After study completion, consenting subjects will continue periodic safety and efficacy assessments for approximately 14 years (for a total of 15 years post-infusion follow-up) in a long-term follow-up study to AVRO-RD-02-201.

3.1. Definition of Study Treatment

The Sponsor identifier for the study drug product is AVR-RD-02. The active substance in AVR-RD-02 is autologous CD34+ enriched HSCs that have been genetically modified ex vivo with an LV containing an RNA transcript that, after reverse transcription, results in codon-optimized cDNA that, upon its integration into the human genome, encodes for functional human GCase. The finished investigational product is presented as a cryopreserved cell suspension in infusion bag(s) in vapor-phase liquid nitrogen, which must be thawed prior to use. The investigational product is intended for one-time IV infusion of between 3×10^6/kg and 10×10^6/kg body weight autologous CD34+ enriched HSCs that have been genetically modified.

In addition to AVR-RD-02, in this study subjects will receive the following auxiliary medications:

- Four to eight G-CSF and two plerixafor injections for HSC mobilization prior to AVR-RD-02 infusion

    - Additional G-CSF injections may be administered beginning Day 30 after treatment with AVR-RD-02 if ANC < 0.5 (10^9/L).
- Anti-convulsant medication administration, concurrent with busulfan administration, for seizure prophylaxis
    - Levetiracetam will be administered. If levetiracetam is contraindicated, an alternative anti-convulsant medication (eg, benzodiazepines or valproic acid) may be used.
- Five IV infusions of busulfan, one test dose to inform the conditioning dose and four for myeloablative conditioning, prior to AVR-RD-02 infusion.

It should be noted that these auxiliary medications are not considered as study treatment.

3.2. Sample Size Considerations

3.2.1. Sample Size Justifications

The sample size of approximately 8 to 16 subjects chosen for this study was selected without statistical considerations, but was determined based on prior Phase 1/2 study designs in Gaucher disease (Barton, 1991; Zimran, 2010).

3.2.2. Sample Size Re-estimation

This is an adaptive study and the study size may increase or decrease based on safety and/or efficacy assessments performed during the course of the study and/or recommendations of the independent DMC and/or regulatory agencies.

3.3. Randomization

This is a non-randomized, open-label study.

3.4. Clinical Assessments

Tabular overviews of the required assessments for the study (including the timing of each) can be found in the Protocol: Schedule of Assessments from Screening through the Apheresis Period, Schedule of Assessments from Investigational Product Preparation and Testing through End of Infusion, and the Schedule of Assessments for the Post-infusion Follow-up Period (Study Week 1 [Day 1] through Study Week 52 [Day 365]).

3.4.1. Primary Efficacy Measures

The following primary efficacy measures will be collected at the times shown in the Protocol:

- Spleen and liver volumes assessed by abdominal MRI. Scans will be performed locally and interpreted by a blinded central reader (local interpretation will be used to determine study eligibility).
- Hemoglobin concentration, hematocrit percentage, and platelet count samples collected for efficacy measures will be tested at a central laboratory.

- Biomarkers for Gaucher disease (ie, chitotriosidase enzyme activity and lyso-Gb1 plasma levels) will be analyzed in blood samples by a central laboratory.

3.4.1. Primary Engraftment Measure

- Blood samples for measurement of average VCN in PBLs and bone marrow aspirate by qPCR and/or ddPCR analysis.

3.4.2. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Protocol:

- GCase enzyme activity level in peripheral blood. Samples will be tested at a central laboratory.
    - Blood collection on DBS cards for GCase activity measurement will also occur at the indicated study time points in mitigation of unforeseen circumstances, which could ruin blood samples arriving out of the sample stability period at the central laboratory.
- ERT frequency and dosing
    - Investigators will record the rationale for initiating standard of care ERT as well as gene therapy infusion dates and dose.
- Anti-GCase total antibodies, and subsequent titers and isotypes.
- BMD assessed by DXA:
    - Scans will be performed and interpreted locally.
- BMB score assessed by bone MRI:
    - Scans will be performed locally and scored by a blinded central reader.
- Chitotriosidase enzyme activity levels in plasma.

3.4.3. Exploratory Efficacy Measures

The following exploratory efficacy measures will be collected at the times shown in the Protocol:

- Functional status assessed by the SF-36:
    - The SF-36 is a 36-item, subject-reported measure yielding 8 subscale scores (Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning, and Mental Health) and 2 component summary scores (Physical Functioning and Mental Functioning)
- Pain assessed by the BPI-SF questionnaire:
    - The BPI-SF is a 9-item self-administered questionnaire used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning on an 11-point scale (ie, 0 = "no pain" to 10 = "pain as bad as you can imagine")

- Exploratory biomarkers for Gaucher disease in serum, plasma, PBLs, and urine: as knowledge of Gaucher disease pathophysiology and related biomarkers continues to evolve, serum, plasma, peripheral blood and urine samples will be collected and archived for possible future non-genomic and genomic biomarker testing.

3.4.4. Safety Measures

3.4.4.1. Primary Safety Measures

Primary safety evaluations to be performed during the study include monitoring of adverse events (AEs) and concomitant medications, clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, measurement of vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

3.4.4.2. Exploratory Safety Measures

Exploratory safety evaluations to be performed during the study include assessments of reproductive potential.

4. PLANNED ANALYSES

4.1. Interim Analysis

In this open-label study, after AVR-RD-02 infusion, measures of engraftment, clinical response, and safety are assessed for each individual subject on an ongoing basis. Also, based on stopping rules and safety data collected from initial enrolled subjects, an independent DMC review at pre-specified intervals will assess the appropriateness of the progressive introduction of additional cohorts and subjects.

Considering this, a discrete interim analysis of data collected in this study will not be performed.

4.2. Final Analysis

The final database lock will occur when all subjects have completed the study (i.e., the final follow-up visit at Week 52 [or prematurely discontinued the study]) and all data are collected and cleaned.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will be prepared according to ICH Guideline E3.

The All Subjects population will be used for specific outputs, as defined below. Safety data will be reported using the Safety and Infused populations, and Efficacy data will be reported using the Infused population.

No treatment-naïve subjects were enrolled, so outputs will only contain switch-stable subjects.

Summary tables for any concomitant medications will be coded according to the World Health Organization (WHO) Drug dictionary Version of WHODrug Global B3 March 2018. Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 23.0.

Missing data will be reported as follows:

- Data captured as 'Unknown', or variations thereof, in the clinical database will be presented as such in the Listings
- Missing data and will be displayed as follows in Listings:
  - 'Not Done' will be presented where a sample was not collected/assessment was not performed (as per EDC)
  - 'No Result' will be presented where the sample was collected/assessment was performed (as per EDC) but no result is available.
  - 'Not Applicable' will be presented when the sample/assessment was not required/expected for that subject/visit, e.g., where a result would only be expected after a protocol amendment but not prior to that amendment.
  - 'Not Calculated' will be presented when no result can be derived, e.g., standard deviation is NC when n<3, or change from baseline (CFB) is NC when no baseline or post-baseline result is available.
- If all data for a specific visit are missing the data are included in the table with N=0.
- Safety assessment values of the form of "< x" (i.e., below the lower limit of quantification (BLQ)) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of descriptive statistics but displayed as "< x" or "> x" in any listings that are produced.
  - If the calculated mean at a sampling time point is BLQ then the mean value will be reported as 'BLQ' and the SD and CV% will be reported as not calculated (NC) in the summary.
    - Similarly, any calculated BLQ values for median, minimum, maximum and geometric mean will be reported as 'BLQ' in the summary.
  - If the calculated mean at a sampling time point is above ULQ then the mean value will be reported as '>ULQ' and the SD and CV% will be reported as not calculated (NC) in the summary.

- Similarly, any calculated values for median, minimum, maximum and geometric mean will be reported as '>ULQ' in the summary.

Imputed dates and times will NOT be presented in the listings. Completely missing start or end dates/times will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. Partial dates/times will be displayed as captured in subject listing displays.

5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The tables and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the individual subject data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The subject disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive subject data listing will be Listing 16.1. Any subset table will have the number Table 14.1.2, etc.

2. Table numbering will follow ICH E3. Subject disposition, baseline and demography and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Efficacy tables will occupy the next sub-level (Table 14.2 series). Safety tables will follow next (Table 14.3 series). Similar conventions will be applied to the subject data listings.

3. Each table and figure title will be complete, accurate and concise. The last line of the title will provide the analysis population being summarized/presented.

4. All analysis and summary tables will include the analysis population sample size (i.e., number of subjects).

5. Each listing title will be complete, accurate and concise. Inclusion in each analysis population will be presented as a flag on selected listings.

6. If possible, variables being summarized and statistics reported will appear in the left most column of a table.

5.3. Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated, where possible. Blank spaces should not be present unless otherwise directed.

All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study participants. The investigative site will make available source documents to any personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source data verification (SDV) of data

entered into the eCRF and raise queries as needed for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated as needed and sent to the investigational site for response before the database is locked and released for statistical analysis.

Data from any screen failures is entered into the clinical database, but this data might not be cleaned. In order to describe the representativeness of the study, this data should be presented including the reasons for screen failures (failure of individual inclusion/exclusion criteria could be presented if appropriate).

Data storage, data transfer and data validation will be conducted according to the relevant [redacted] Standard Operating Procedures (SOPs).

Following database lock, data will be shared with the AVROBIO, Inc. Biostatistics Department for programming of analysis datasets, tables, listings, and figures. All SAS® programs used to create analysis datasets and outputs will be validated by ensuring that the ".log" files are void of all errors, warnings, and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs will be developed and validated through risk-based quality control by the AVROBIO, Inc. Biostatistics Department.

Outputs will include data extraction date. The purpose of the data extraction date is to link the output to the database, either active or archived, that is write-protected for replication and future reference. The program execution date will appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table(s) and figure(s).

Table 2: Laboratory data vendors

Vendor Name	Assay	Parameter (Units)	LLD[1]	LLQ[1]	ULQ[1]	LLN[1]	ULN[1]
[redacted]	GCase enzyme activity (PBLs)	µmol/g/h	NA	0.3	100.0	4.0	NA
	GCase enzyme activity(plasma)	µmol/L/h	NA	0.2	200.0	0.4	NA
	GCase enzyme activity (DBS card)	µmol/g/h	NA	1.0	200.0	4.1	NA
	Chitotriosidase Enzyme Activity	µmol/L/h	NA	0.8	150.0	NA	38.1
	Lyso-Gb1 (plasma)	ng/mL	NA	0.6	1000.0	NA	1.2
	GBA gene sequence	NA[2]	NA	NA	NA	NA	NA
	CHIT1 gene sequence	NA[2]	NA	NA	NA	NA	NA

[redacted]	VCN (peripheral blood)	average copies/cell	NA	0.0027	NA	NA	0.0
	anti-GCase antibody titer	ng/mL	5.33[3]	15.9[3]	NA	NA	0.0
[redacted]	Replication competent lentivirus	NA[2]	NA	NA	NA	NA	NA
[redacted]	Insertion site analysis	NA[2]	NA	NA	NA	NA	NA

[1] LLD = Lower Limit of Detection; LLQ = Lower Limit of Quantification; LLN = Lower Limit of Normal; ULN = Upper Limit of Normal

[2] This method does not generate quantitative results.

[3]Sensitivity was established both for screening and confirmatory runs. The LLD represented the lower limit used for the screening run. The LLQ represents the lower limit used for the confirmatory run. This arrangement reduces the potential for type I errors.

5.4. Data Presentation Conventions

The following conventions will apply for data presentation:

- All listings will be produced using the All Subjects population;
- Continuous safety variables will be reported to the same precision as the source data. Derived variables will be reported using the same precision as the value(s) from which they were derived. For the reporting of descriptive statistics, the mean, median, standard deviation and CV% will be reported to 1 decimal place more than the source data; the minimum and the maximum values will be presented to the same precision as the source data;
- For categorical/discrete variables, the frequency count and the percentage (of available data) for each category of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. The denominator for all percentages will be the number of subjects with non-missing data within the analysis population of interest. Otherwise, percentages (for example for AEs and Concomitant Medications) will be calculated based on the population total. If the analysis population is not stated in the title then a footnote will clarify the denominator used. A row denoted 'Missing' will be included in count tabulations to account for dropouts and missing values;
- All percentages will be rounded to one decimal place. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0). In the case the numerator is equal to 0, the percentage will not be presented;

- Date variables will be formatted as DD-MMM-YYYY for presentation. Time will be formatted in military time as HH:MM for presentation;
- Unscheduled assessments will be considered when applying visit windows and derived study periods and will also contribute to the end of study value, or best/worst case value where required (e.g., shift table);
- When deriving a subject level statistic (e.g., maximum value post-baseline), all values should be included regardless of whether they appear in a corresponding visit-based summary;
- All listings will be sorted for presentation in order of subject, parameter, and date/time of procedure or event.
- Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once upon discussion between the Investigator and Medical Monitor.
    - Where a re-screened subject is present in the clinical database under two different identifiers, data will be combined for Tables and Figures, and the identifiers will be concatenated for Listings with a footnote included to describe the details of re-screening.
- For medical/surgical history and AEs, frequency ordering will be used for the summary table presentation (i.e., order by the overall grouping in descending frequency, and then alphabetical order in the case of equal frequency, for each System Organ Class (SOC) and also for each Preferred Term (PT) within each SOC). Columns that are used for grouping in descending frequency will be specified in the footnote;
    - TEAEs will be presented in descending order of frequency across all subjects.
- Outputs will define Lower Limit of Quantification (LLQ) and Upper Limit of Quantification (ULQ) values, including the units, if applicable;
    - Values below the LLQ (BLQ), or not detected or not quantifiable, will be imputed as the LLQ (where available) or as 0.01 for figures and for summary statistics, and n imp, the number of imputed values, will be reported;
    - Values above the ULQ will be imputed as the ULQ (where available) for figures and for summary statistics, and n imp, the number of imputed values, will be reported;
    - Imputed values will be used for Tables and Figures, but Listings will present the original values
- Outputs will define Lower Limit of Detection (LLD) values, including the units, if applicable;
- Outputs will include reference ranges and Normal Ranges, including the units, if applicable;
- Outputs will include units, if applicable;

- On all plots with time on the x-axis, the spacing of the x-axis timepoints will be on a continuous scale and will reflect actual time between visits, if spacing permits;
- On all plots, where a mean line is included, a dashed black line (thickness greater than the individual subject lines) will be used;
- A month is counted as 30.4375 days and a year is counted as 365.25 days (30.4375 days × 12 months);
- Summary statistics:
    - Summary statistics for efficacy data (absolute values) will include N, n, geometric mean, coefficient of variation between subjects (%CVb), median, minimum, and maximum will be reported (where n<3, only mean, median, minimum and maximum will be presented);
        - Geometric Mean will be presented when at least 3 values (including imputed values) are available;
        - %GeoCV will be calculated as: $100 * (e^{\mathrm{sd}(\log(X))} - 1)$;
    - Summary statistics for safety data, and for changes from baseline, will include N, n, mean, SD, minimum, median, and maximum will be reported (where n<3, only mean, median, minimum and maximum will be presented);
- For plots of log-normal data, the y-axis may be presented on the log-scale, as required;

Outputs will be delivered as pdf and rtf format.

5.5. Analysis Populations

Subject inclusion into each population will be determined before database lock and prior to commencing the final analysis.

5.5.1. All Subjects Population

The All Subjects population will consist of all subjects who consented, i.e. were enrolled.

All listings will be produced using the All Subjects population.

5.5.2. Safety Population

The Safety population will consist of all enrolled subjects who receive any auxiliary medication (G-CSF, plerixafor, busulfan, or anti-convulsant) or AVR-RD-02. This population will be used for the summaries of all safety data.

5.5.3. Infused Population

The Infused population will consist of all enrolled subjects who receive all auxiliary medications and AVR-RD-02. This population will be used for the summaries of all efficacy and safety data.

5.6. Baseline Definition

For all **safety and efficacy endpoints**, Baseline (Derived) will be defined as the last available, non-missing observation prior to first administration of an auxiliary medication (G-CSF, plerixafor, busulfan, or anti-convulsant) or AVR-RD-02, unless specifically mentioned otherwise.

Non-numeric (i.e., categorical) observations will be considered for baseline calculations, where applicable. In addition, non-missing results from unscheduled assessments prior to first administration of an auxiliary medication may also be considered in the calculation of baseline observations.

If more than one assessment is collected first administration of an auxiliary medication or AVR-RD-02 infusion and it is not possible to determine which is the closest then the mean of the assessments will be used as Baseline (Derived).

Where baseline values are at or below the LLQ (BLQ), or not detected or not quantifiable, these will be imputed as the LLQ (where available) or as 0.01 for figures and for summary statistics.

Likewise, values above the ULQ will be imputed as the ULQ (where available) for figures and for summary statistics.

Baseline (Derived) will be defined as a footnote on each applicable output.

Listings, Tables and Figures will present all visits and Baseline (Derived), however, figures and shift tables presenting change from baseline (CFB) or percent change from baseline (%CFB) will only include Baseline (Derived) and post-baseline visits only.

5.7. Derived and Transformed Data

The SAP includes all derivations that are necessary for the analysis and reporting of the study. Any handling rules for source data (from the eCRF or from a third-party vendor) and derived data are detailed in this SAP. Any endpoints that already have the derivation performed in the source data, and therefore need no further programmatic derivation, are identified as such.

5.7.1. Age at Screening

Age, in completed years, at screening will be defined as:

Age (years) = floor value ((Date (first) signed Informed Consent – Date of Birth + 1) / 365.25)

5.7.2. Body Mass Index

Body Mass Index (kg/m^2, to one decimal place) = Body Weight (kg) / (Height x Height (m))

5.7.3. Study Day

Study Day will be defined as:

Study Day = Date of Assessment – Date of AVR-RD-02 infusion (if date of assessment is before Date of AVR-RD-02 infusion)

Otherwise,
Study Day = (Date of Assessment – Date of AVR-RD-02 infusion) + 1

For any population which includes subjects who may not have received AVR-RD-02, e.g., the Safety population, the Study Day will not be derived, except where the SAP indicates date of (first) signing of informed consent is used.

5.7.4. Study Week

Study Week will be defined as:

Study Week = floor value [(Study Day / 7) + 1]

5.7.5. Time since AVR-RD-02 Infusion

Time since AVR-RD-02 infusion will be calculated as**:**

$$Time\ Since\ \text{AVR} - \text{RD} - 02\ \ (months) = \frac{Study\ Day}{30.4375}$$

5.7.6. Age at enrollment

Age at enrollment will be calculated as:

$$Age\ at\ Enrollment\ (months) = \frac{(Date\ of\ (first)\ Informed\ Consent - Date\ of\ Birth)}{30.4375}$$

5.7.7. Age at AVR-RD-02 infusion

Age at AVR-RD-02 infusion will be calculated as:

$$Age\ at\ \text{AVR} - \text{RD} - 02\ Infusion\ (months) = \frac{Date\ of\ Infusion - Date\ of\ Birth}{30.4375}$$

5.7.8. Adverse event onset time relative to AVR-RD-02 infusion

Adverse event onset time relative to AVR-RD-02 infusion will be calculated as:

Adverse event onset time relative to AVR-RD-02 infusion = Onset Date and Time of AE – AVR-RD-02 infusion Date and Time, if onset date of AE is before Date of AVR-RD-02 infusion

Otherwise, Adverse event onset time relative to AVR-RD-02 infusion = (Onset Date and Time of AE – AVR-RD-02 infusion Date and Time) + 1

Where time is missing, only dates will be used. Refer to Section 5.7.15 for handling of incomplete dates.

5.7.9. Duration of Adverse Events

Duration of Adverse Events (in DD:HH:MM) will be calculated as:

Duration of Adverse Event = (Resolution Date and Time) – (Onset Date and Time)

Where time is missing, only dates will be used. If a resolution or onset date is missing or incomplete, no duration will be derived.

5.7.10. Change from Baseline

For safety and efficacy, CFB will be calculated as (post-baseline result – baseline result), and percentage change from baseline (%CFB) will be calculated as 100 x (post-baseline result – baseline result)/baseline result.

Changes from baseline will use Baseline (Derived), including where Baseline (Derived) uses the imputed LLQ value.

Change from baseline comparisons for categorical variables will use Baseline (Derived) and will be displayed using shift-tables that display the frequency and percentage of subjects within each category at baseline and at any specified time points.

If Baseline (Derived) is missing then the CFB and %CFB will also be set to missing, unless otherwise stated. Only subjects with a value at both the Baseline (Derived) visit and the specific post-baseline visit will be presented.

5.7.11. Observed Cases (OC) and Last Observation Carried Forward (LOCF) and Outliers

Not applicable for this study. Missing data will not be imputed.

Outliers will be included in all outputs.

5.7.12. Completers

Not applicable for this study.

5.7.13. SF-36

SF-36 version 2 will be used in the study and will be scored as per the instructions for the RAND 36-Item Health Survey 1.0 - (https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html).

There are eight health domains (Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning and Mental Health) and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. Scoring will be undertaken using the commercial software by QualityMetric. The scores provided by QualityMetric will be used for the data summary.

5.7.14. BPI-SF

Two scores are calculated from the Brief Pain Inventory - (https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf).

The pain severity score is calculated as the mean of the non-missing values for questions 3 (worst pain), 4 (least pain), 5 (average pain) and 6 (current pain).

The pain interference score is calculated as the mean of the non-missing values for questions 9a, b, c, d, e, f and g, which represent pain interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Subjects who answer fewer than four questions will not have a pain interference score derived.

5.7.15. Derivations for Adverse Events

A treatment-emergent adverse event (TEAE) will be any adverse event occurring after a subject has started auxiliary medications, i.e., started mobilization with G-CSF. This includes: i) any AE that emerges after start of mobilization with G-CSF (having been absent before start of mobilization with G-CSF) or ii) any AE that although present before G-CSF, worsens after start of mobilization with G-CSF (in this case, there will be a new AE entered after worsening).

Where the start date/time of an AE is partial or missing and the end date/time is on or after the date/time of start of mobilization with G-CSF, or both the start and end dates/times are missing, then a "worst-case" scenario will be assumed, thus the AE is assumed to have occurred after the start of mobilization with G-CSF (i.e., treatment-emergent) unless a partial start or end date indicates otherwise. When partial dates are present in the data, both a partial start date and/or a partial end date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of mobilization with G-CSF or ended prior to the start of mobilization with G-CSF. If it cannot be conclusively established that the AE started prior to the start of mobilization with G-CSF based on the partial start and/or end dates, then the AE will be considered as treatment-emergent.

The following table presents an algorithm for the determination of whether a given AE will be considered treatment emergent or not:

Table 3: Algorithm for Treatment Emergence of Adverse Events

Start date of AE	**End date of AE**	**Action**
Known	Known, Partial or Missing	If start date/time < start date/time of mobilization with G-CSF, then not TEAE Otherwise, if start date/time ≥ mobilization with G-CSF start date/time, then TEAE
Partial, but known components show that it cannot be on or after mobilization with G-CSF start date/time	Known, Partial or Missing	Not TEAE
Partial, could be on or after mobilization with G-CSF start date/time OR Missing	Known	If end date/time < mobilization with G-CSF start date/time, then not TEAE If end date/time ≥ mobilization with G-CSF start date/time, then TEAE
	Partial	Temporarily impute end date/time as latest possible date/time (i.e., 23:59 on last day of month if day and time unknown or 31st

Start date of AE	End date of AE	Action
		December 23:59 if day and month and time are unknown), then: If imputed end date/time < mobilization with G-CSF start date/time, then not TEAE If imputed end date/time ≥ mobilization with G-CSF start date/time, then TEAE
	Missing	Assumed TEAE

These imputations will only be used to determine treatment emergence for inclusion in table summaries; the reported missing or partial dates will be presented in listings.

AEs will be tabulated by one of the seven study periods based on the onset date/time of AEs:

- Pre-Mobilization: started before first dosing of G-CSF
- Auxiliary Medications:
    - Mobilization:
        - G-CSF: started (or worsened) on or after first dosing of G-CSF for Mobilization until start of apheresis
            - For any subject who received Mobilization twice, the study period between the start of the second Mobilization until the start of the second apheresis will be captured as Mobilization #2
    - Apheresis:
        - started (or worsened) on or after start of apheresis until the end of the last apheresis
            - For any subject who received Apheresis twice, the study period between the start of the second apheresis until the end of the second apheresis will be captured as Apheresis #2
    - Post-Apheresis: started (or worsened) after the end of the last apheresis and before first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan
        - For any subject who received Mobilization twice, the study period between the end of the first apheresis and the start of Mobilization #2 will be captured as Post-Apheresis
            - The study period between the end of the second apheresis and the first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan will be captured as Post-Apheresis #2

        - For any subject who received Mobilization but did not proceed to receive conditioning or AVR-RD-02, the study period after the end of Apheresis will be captured as Post-Apheresis
    - Conditioning: started (or worsened) on or after first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan and before infusion of AVR-RD-02
- AVR-RD-02 Infusion: started (or worsened) on or after the start of infusion of AVR-RD-02
- Post-AVR-RD-02 Infusion Follow-Up: started (or worsened) after the end of AVR-RD-02 infusion

The date and time of AEs are captured, as well as date and time for G-CSF, plerixafor, apheresis, busulfan and AVR-RD-02 infusion. Therefore, when assigning AEs to a study period, the time (HH:MM) of the onset (or worsening) of the AE will be compared to the time of the auxiliary medication or AVR-RD-02, e.g., on Day 1, an AE with onset time prior to the start time of AVR-RD-02 infusion will be assigned to the Conditioning study period. Where time is missing or incomplete, the AE will be assigned to the study period using the date alone, e.g., on Day 1, an AE on Day 1 with onset time missing will be assigned to the AVR-RD-02 infusion study period.

If an adverse event continues into subsequent periods it will only be counted in the period in which it first occurred, in order to avoid double counting.

6. TREATMENT COMPARISONS

6.1. Data Display Treatment and Other Sub-Group Descriptors

The Analysis Population used will be presented on all figures and tabulations.

Adverse Events will be summarized by System Organ Class (SOC) and Preferred Term (PT). Additionally, AEs will be summarized by study period (Pre-Mobilization, Auxiliary Medications, AVR-RD-02 Infusion, and Post-AVR-RD-02 Infusion Follow-Up). The Auxiliary Medications study period will be further broken down into Mobilization, Apheresis, Post-Apheresis, and Conditioning. The following labels for study period will be used on applicable AE tabulations:

- All Adverse Events
- Pre-Mobilization
- Auxiliary Medications
  - Mobilization
    i. Mobilization #2 for any subject who received Mobilization twice
  - Apheresis
    i. Apheresis #2 for any subject who received Apheresis twice
  - Post-Apheresis
    i. Post-Apheresis #2 for any subject who received Mobilization/Apheresis twice
- Conditioning
- AVR-RD-02 Infusion
- Post-AVR-RD-02 Infusion Follow-Up

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings and summary tables for the disposition, safety and efficacy data will be the responsibility of the study Biostatistician.

The currently supported version of SAS® software will be used to perform all data analyses. The actual SAS® version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by subject number and assessment date/time. In the listings, subject number will be of the format 123456.

7.1. Multicenter Studies

Data from all participating sites will be pooled.

7.2. Other Strata and Covariates

Not applicable for this study.

7.3. Examination of Subgroups

Not applicable for this study.

7.4. Multiple Comparisons and Multiplicity

Not applicable for this study as there are no formal hypothesis tests being conducted.

7.5. Data handling conventions

7.5.1. Premature Withdrawal and Dropouts

For subjects who are withdrawn or dropout from the study prior to study completion, all data collected will be listed and included in data summaries. Early termination data will be mapped using visit windows.

7.5.2. Additional/Unscheduled Assessments

Generally, missing dates/times will not be imputed. Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified based on the study period closest to the AE onset. Adverse events will be assigned to each study period according to Section 5.7.15.

Unscheduled assessments will be considered when applying visit windows (and for derived study periods) and will also contribute to the end of study value, or best/worst case value where required (e.g., shift table).

When deriving a subject level statistic (e.g., maximum value post-baseline), all values should be included (including scheduled, unscheduled, retest and early discontinuation data) regardless of whether they appear in a corresponding visit-based summary.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.5.3. Assessment Windows

Visit windows as defined below will be applied and applied in tables and/or figures:

Table 4: Visit Window Assignment

Assigned Study Day (Inclusive)		Visit Assigned	Target Study Day	Target Study Week
From	To			
1	1	Day 1 (Transplant)	1	1
2	2	Day 2 (W1)	2	1
3	3	Day 3 (W1)	3	1
4	4	Day 4 (W1)	4	1
5	5	Day 5 (W1)	5	1
6	6	Day 6 (W1)	6	1
7	7	Day 7 (W1)	7	1
8	12	Day 10 (W2)	10	2
13	22	Day 14 (W2)	14	2
23	45	Day 30 (W5)	30	5
46	75	Day 60 (W9)	60	9
76	105	Day 90 (W13)	90	13
106	135	Day 120 (W18)	120	18
136	165	Day 150 (W22)	150	22
166	225	Day 180 (W26)	180	26
226	318	Day 270 (W39)	270	39
319	413	Day 365 (W52)	365	52

Inclusion within the time window should be based upon the actual date of the visit rather than the intended date so that all unscheduled visit data (including unscheduled early termination visits) have the potential to be included.

In the case where two or more measurements fall within the same visit window, the available measurement closest to the planned visit date will be used. If two measurements are equidistant from the planned visit date then the earlier value will be used. If multiple measurements occurred on the same date, and the time (HH:MM) of each assessment is available, then these will be reviewed on a case-by-case basis. If time is unavailable, the mean of the measurements will be taken. In the case of a retest where there is clear evidence to suggest that the retest was done due to erroneous data, then the retest value will be used. Otherwise, the mean of the measurements will be used.

Scheduled, unscheduled, retest and early discontinuation data will be included when mapping to visit windows.

7.5.4. Visit/Study Period Mapping and Labels

Within **Tables**, **Figures** and **Listings**, the mapping and derived visit labels in Table 4 will be used from date of AVR-RD-02 infusion onwards.

In order to aid interpretation of the temporal nature of adverse events and medications, derived study periods are applied. If it is deemed necessary for other data, eg clinical laboratory values, vital signs, etc., then derived study periods will also be applied as described below.

Prior to the date of AVR-RD-02 infusion, the below mapping and derived study period labels will be used in **Listings**:

- Pre-Mobilization: date is before first dosing of G-CSF for Mobilization
- Auxiliary Medications:
    - Mobilization:
        - G-CSF: started (or worsened) on or after first dosing of G-CSF for Mobilization until start of apheresis
            - For any subject who received Mobilization twice, the study period between the start of the second Mobilization until the start of the second apheresis will be captured as Mobilization #2
    - Apheresis:
        - started (or worsened) on or after start of apheresis until the end of the last apheresis
            - For any subject who received Apheresis twice, the study period between the start of the second apheresis until the end of the second apheresis will be captured as Apheresis #2
    - Post-Apheresis: started (or worsened) after the end of the last apheresis and before first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan
        - For any subject who received Mobilization twice, the study period between the end of the first apheresis and the start of Mobilization #2 will be captured as Post-Apheresis
            - The study period between the end of the second apheresis and the first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan will be captured as Post-Apheresis #2
        - For any subject who received Mobilization but did not proceed to receive conditioning or AVR-RD-02, the study period after the end of Apheresis will be captured as Post-Apheresis
    - Conditioning: date is on or after first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan and before date of infusion of AVR-RD-02

Listings will present both protocol visit/study day and also derived study period/study day. Baseline (Derived) will also be included. Unscheduled, retest and early discontinuation data prior to the day of AVR-RD-02 infusion will be included when mapping to the above study period labels for **Listings**.

In **Tables** and **Figures**, the following mapping and study period labels will again be used prior to the day of AVR-RD-02 infusion:

- Pre-Mobilization: date is before first dosing of G-CSF for Mobilization
- Auxiliary Medications:
    - Mobilization:
        - G-CSF: started (or worsened) on or after first dosing of G-CSF for Mobilization until start of apheresis
            - For any subject who received Mobilization twice, the study period between the start of the second Mobilization until the start of the second apheresis will be captured as Mobilization #2
    - Apheresis:
        - started (or worsened) on or after start of apheresis until the end of the last apheresis
            - For any subject who received Apheresis twice, the study period between the start of the second apheresis until the end of the second apheresis will be captured as Apheresis #2
    - Post-Apheresis: started (or worsened) after the end of the last apheresis and before first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan
        - For any subject who received Mobilization twice, the study period between the end of the first apheresis and the start of Mobilization #2 will be captured as Post-Apheresis
            - The study period between the end of the second apheresis and the first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan will be captured as Post-Apheresis #2
        - For any subject who received Mobilization but did not proceed to receive conditioning or AVR-RD-02, the study period after the end of Apheresis will be captured as Post-Apheresis
    - Conditioning: date is on or after first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan and before date of infusion of AVR-RD-02

For **Tables** and **Figures**, scheduled, unscheduled, retest and early discontinuation data will be included when mapping to study periods. In the case where daily measurements were not scheduled per protocol, but two or more measurements still fall within the same study period, then these will be reviewed on a case-by-case basis. In the case of a retest where there is clear evidence to suggest that the retest was done due to erroneous data, then the retest value will be used.

In the case where daily measurements were scheduled per protocol, e.g., daily measurements during Mobilization, Apheresis or Conditioning, then each individual scheduled assessment will be included separately in **Tables** and **Figures** under the appropriate study period label, e.g. Mobilization (Day 1).

Baseline (Derived) will also be included in all **Tables** and **Figures**.

Figures presenting CFB for efficacy will only include Baseline (Derived) and post-AVR-RD-02 visits derived as per Table 4.

Figures presenting CFB for safety will include Baseline (Derived) and post-baseline visits.

Shift Tables presenting shifts from baseline for safety will include Baseline (Derived) and post-baseline visits.

For subjects who are withdrawn or dropout from the study prior to study completion, all data collected will be listed and included in tables and/or figures. Early termination data will be mapped using visit windows to the derived visits in Table 4 or to the derived study periods described above.

7.6. Derived and Transformed Data

The required endpoints and variables will be derived by the statistical programmers at AVROBIO, Inc. using the derivations specified in Section 5.7 of this SAP.

8. STUDY POPULATION

All disposition, baseline and demographic data will be listed using the All Subjects population.

8.1. Disposition of Subjects

A disposition listing will present date of informed consent, date of enrollment, date of study completion or early termination, the primary reason for early discontinuation, if applicable, duration of follow-up (using time since AVR-RD-02 infusion), if applicable, and whether included in each population and reasons for exclusion, for each subject.

A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by subject, will also be presented.

8.2. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that occur during the conduct of a clinical study (ICH E3 Questions and Answers). Protocol deviations should be defined as either "Important protocol deviations" (IPDs) per the ICH E3 guidance "Structure and content of clinical study reports" or "Other Study Deviations". Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being, and include:

- Any clinical condition that in the Investigator's opinion could become dangerous for the subject and prevent the good conduct of the clinical trial;
- Protocol violation that could compromise the quality of study data such as: use of erythropoietin, use of biological agents potentially modifying erythropoiesis, enrolment into interventional clinical trials, bone marrow transplantation;
- Occurrence of new diseases that could influence the treatment efficacy, for which AVRO-RD-02 is contraindicated or that are treated with a medication that is not permitted as a concomitant medication.

The process of identifying protocol deviations as well as identification of IPDs, review and classification are specified in the Protocol Deviation Management Plan.

The need for any supplementary analyses resulting from protocol deviations will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

The Sponsor or designee will be responsible for producing the final protocol deviation file in collaboration with [redacted] and the data monitoring group as applicable; this file will include a description of the protocol violation and clearly identify whether or not this violation warrants exclusion from the aforementioned populations.

All protocol deviations will be listed. The type of protocol deviation, the description, importance and classification, actions taken, and the date it occurred will be included. The potential impact of notable protocol deviations deemed important by the study team will be discussed in the CSR.

8.3. Demographic and Baseline Characteristics

All baseline and demographic data recorded at screening and prior to dosing will be listed.

Subject demographic and baseline characteristics will include age at enrollment, age at AVR-RD-02 infusion, gender, race, ethnicity, height, body weight, BMI, GCase enzyme in peripheral blood, GCase enzyme in DBS, GCase enzyme in plasma, Lyso-Gb1 concentration in plasma, and Chitotriosidase enzyme in plasma.

Data listings will also be provided for:

- Diagnosis information, including age at time of diagnosis and age at onset of symptoms
- Historical mutation analysis
- Transmittable disease testing
- Prior ERT, SRT, and other prior treatments

8.4. Medical History and Medical Conditions Present at Entry

All medical history conditions, concomitant diseases and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using MedDRA® v23.0 . The version will be labelled in the applicable outputs.

Past and current medical conditions will be listed, including whether the subject has experienced any past concomitant diseases or surgeries, start date, end date or whether it is ongoing, the disease or symptom, the SOC and PT, the maximum CTCAE Grade, and whether it resulted in hospitalization.

8.5. Extent of Exposure

AVR-RD-02 infusion drug product characteristics will be obtained from the Certificates of Analysis (CoA).

8.6. Treatment Compliance

All auxiliary medication administration data (G-CSF, plerixafor, busulfan, and anti-convulsant) and AVR-RD-02 infusion will be listed. Apheresis data (e.g., total cell count, CD34+ cell count) will also be listed.

The listing of busulfan will include the dose administered each day, percentage dose increased/decreased vs. the previous dose, percentage difference between expected and actual dose, the start and end times, total dose (mg), body surface area (m^2) and total dose/BSA (mg/m^2), AUC and Total AUC.

The listing of AVR-RD-02 infusion will include start date and time of infusion, end date and time of infusion, subject weight (kg), total volume infused (mL) and date of initial hospital discharge. If more than one batch of gene therapy was manufactured and administered to the subject, then the sum will also be presented for total volume infused (mL).

A listing will include the dates and derived study day of:

- G-CSF for Mobilization
  - Excludes any G-CSF injections administered after treatment with AVR-RD-02 for hematological reconstitution due to ANC < 0.5 (10^9/L), which will be listed separately
- Plerixafor
- Apheresis
- Anti-convulsant medication given for prophylaxis ahead of busulfan
- Conditioning with busulfan
- AVR-RD-02 infusion

Since all the above-mentioned administrations will be done at the investigational site, treatment compliance will not be determined for this study.

8.7. Prior and Concomitant Medications

The end dates of medications will be used to assign medications into different categories:

- Prior medication: Prior medications are defined as any medication where the use was stopped prior to the first administration of G-CSF for Mobilization.
- Concomitant medication: Concomitant medications are defined as any medication (other than the auxiliary medications and AVR-RD-02) that was used at least once after the first administration of G-CSF for Mobilization. Medications that were stopped on the same date as G-CSF will be defined as concomitant medications. The answer to the question "Ongoing?" as recorded on the eCRF pages will also be taken into consideration to determine if a medication is classed as concomitant.

Table 5 below shows the algorithm for Prior/Concomitant Medications. For the purposes of the below algorithm, note that if the start date is partial then the start date should be temporarily imputed as the earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and if the end date is partial then the end date should be temporarily imputed as the latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown):

Table 5: Algorithm for assignment of timing for medication use

Start date	End date	Action
Known	Known, Partial or Missing	If end date < start date of mobilization with G-CSF, then not Concomitant Otherwise, if end date ⩾ mobilization with G-CSF start date, then Concomitant

Start date	End date	Action
Partial, but known components show that it cannot be on or after mobilization with G-CSF start date	Known, Partial or Missing	Not Concomitant
Partial, could be on or after mobilization with G-CSF start date OR Missing	Known	If end date < mobilization with G-CSF start date, then not Concomitant If end date ⩾ mobilization with G-CSF start date, then Concomitant
	Partial	Temporarily impute end date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If imputed end date < mobilization with G-CSF start date, then not Concomitant If imputed end date ⩾ mobilization with G-CSF start date, then Concomitant
	Missing	Assumed Concomitant

The start dates and end dates of prior and concomitant medications will be used to further split prior and concomitant medications into the following periods:

- Pre-Mobilization: ended before first dosing of G-CSF
- Auxiliary Medications:
    - Mobilization:
    - G-CSF: started on or after first dosing of G-CSF for Mobilization and before start of apheresis
        - For any subject who received Mobilization twice, the study period between the start of the second Mobilization until the start of the second apheresis will be captured as Mobilization #2
    - Apheresis:
    - started on or after start of apheresis until the end of the last apheresis

        - For any subject who received Apheresis twice, the study period between the start of the second apheresis until the end of the second apheresis will be captured as Apheresis #2
    - Post-Apheresis: started after the end of the last apheresis and before first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan
        - For any subject who received Mobilization twice, the study period between the end of the first apheresis and the start of Mobilization #2 will be captured as Post-Apheresis
            - The study period between the end of the second apheresis and the first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan will be captured as Post-Apheresis #2
        - For any subject who received Mobilization but did not proceed to receive conditioning or AVR-RD-02, the study period after the end of Apheresis will be captured as Post-Apheresis
    - Conditioning: started on or after first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan and before date of AVR-RD-02 infusion
- AVR-RD-02 Infusion: started on or after the start of infusion of AVR-RD-02
- Post-AVR-RD-02 Infusion Follow-Up: started after the end of AVR-RD-02 infusion

Note since only dates are captured for medications, and not times, that the start/end dates will be used to assign medications to a period, e.g., a medication starting on Study Day 1 will be assigned to the AVR-RD-02 infusion period because it is not known if the medication started before or after the start time of the AVR-RD-02 infusion on Day 1.

Medications will be classified as a prior medication and/or a concomitant medication. The prior and concomitant medications are exclusive with each other. The same concomitant medication, however, could appear in multiple periods of Mobilization, Apheresis, Post-Apheresis, Conditioning, AVR-RD-02 Infusion, and Post-AVR-RD-02 Infusion Follow-Up, if it was used in two or more of those periods.

Prior and concomitant medications do not include G-CSF, plerixafor, busulfan, and anti-convulsant medication administration for seizure prophylaxis. However, any G-CSF administered due to ANC < 0.5 (10^9/L), beginning Day 30 after treatment with AVR-RD-02, will be listed separately.

Similarly, any platelet transfusions will be listed separately.

Prior and concomitant medications will be coded by WHODrug Global B3 March 2018.

Prior medication and concomitant medications will be listed. The period and within period study day for medication start and stop and all periods where the medication has been used will be provided. For concomitant medications, medication name, product name, start dates and end dates, dose, dose unit, frequency, route, and indication (including details of any associated MH or AE) will be presented. Concomitant medications which started prior to a subject's first auxiliary medication will be flagged.

The auxiliary medications (G-CSF, plerixafor, busulfan, or anti-convulsant) will be listed separately (see Section 8.5).

Listings will be sorted by subject identification number and start date. If the start date is completely missing, then these events will be presented first. If the onset date is missing a month or a day then partial dates for medications will be imputed as per Table 5 to allow medications to be sorted appropriately. Imputed dates will not be listed.

9. EFFICACY ANALYSES

All efficacy analyses will be conducted on the Infused population.

9.1. Primary Efficacy Analysis

9.1.1. Spleen and Liver Volume

All spleen and liver volumes will be listed, together with %CFB. For spleen volume, any increase from baseline ≥25%, and for liver volume, any increase from baseline ≥20%, will be flagged on the listing.

Figures displaying %CFB over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided. For spleen volume, a horizontal reference line will be added to indicate a 25% increase from baseline, and for liver volume, a horizontal reference line will be added to indicate a 20% increase from baseline.

9.1.2. Hemoglobin Concentration

Observed values and absolute change from baseline in hemoglobin values will be listed. Any decreases from baseline of >2 (g/dL) will be flagged on the listing.

Hemoglobin values relative to baseline, derived as post-baseline value/baseline value, will also be listed, and any values <0.8, indicating hemoglobin concentrations < 80% of the baseline value, will be flagged on the listing.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided. A horizontal reference line will be added to indicate a CFB of -2 (g/dL).

A figure displaying individual values relative to baseline over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided. A horizontal reference line will be added at 0.8 to indicate any hemoglobin concentration < 80% of the baseline value.

9.1.3. Platelet Count

Platelet counts will be listed. Any values <35 (10^9/L) will be flagged on the listing.

Platelet counts relative to baseline, derived as post-baseline value/baseline value, will also be listed, and any values <0.8, indicating platelet count < 80% of the baseline value, will be flagged on the listing.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided. A horizontal reference line will be added at 35 (10^9/L).

A figure displaying individual values relative to baseline over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided. A horizontal reference line will be added at 0.8 to indicate any platelet count < 80% of the baseline value.

9.1.4. Lyso-Gb1 in Plasma

Observed values and absolute change from baseline in Lyso-Gb1 plasma levels will be listed. Any values >1.2 ng/mL will be flagged on the listing.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided.

A horizontal reference line will be added at the ULN of 1.2 ng/mL.

Dashed horizontal reference line will be added at the LLQ of 0.6 ng/mL and at the ULQ of 1000 ng/mL.

9.2. Primary Engraftment Analysis

9.2.1. VCN in Peripheral Blood

VCN in peripheral blood assessed by qPCR will be listed.

A figure displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means.

A horizontal reference line will be added at the LLQ of 0.0027 average copies/cell.

9.2.2. VCN in Bone Marrow Aspirate

VCN in bone marrow stem and progenitor cells assessed by qPCR will be listed.

A figure displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means.

A horizontal reference line will be added at the LLQ of 0.0027 average copies/cell.

9.3. Secondary Efficacy Analyses

9.3.1. GCase Enzyme Activity in Peripheral Blood, DBS and Plasma

Observed values and absolute change from baseline in GCase enzyme activity level values in peripheral blood, plasma and DBS will be listed.

For GCase enzyme activity level values in peripheral blood, any values <4.0 µmol/g/h will be flagged on the listing.

For GCase enzyme activity level values in plasma, any values <0.4 µmol/L/h will be flagged on the listing.

For GCase enzyme activity level values in DBS, any values <4.1 µmol/g/h will be flagged on the listing.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided for peripheral blood, plasma and DBS.

On the figure of absolute values of GCase enzyme in peripheral blood, a horizontal reference line will be included at the LLN (4.0 µmol/g/h) and at 15% of LLN (0.6 µmol/g/h). Dashed

horizontal reference lines will be included at the LLQ (0.3 µmol/g/h) and the ULQ (100 µmol/g/h).

On the figure of absolute values of GCase enzyme in plasma, a horizontal reference line will be included at the LLN (0.4 µmol/L/h) and at 15% of LLN (0.06 µmol/L/h). Dashed horizontal reference lines will be included at the LLQ (0.2 µmol/L/h) and at the ULQ (200 µmol/L/h).

On the figure of absolute values of GCase enzyme in DBS, a horizontal reference line will be included at the LLN (4.1 µmol/g/h) and at 15% of LLN (0.615 µmol/g/h). Dashed horizontal reference lines will be included at the LLQ (1.0 µmol/g/h) and at the ULQ (200 µmol/g/h).

9.3.2. ERT

The rationale, frequency, and doses of ERT, including between Weeks 26-52 (inclusive) will be listed.

9.3.3. Immunogenicity

All individual immunogenicity data will be presented in data listings, including the presence or absence of anti-GCase antibodies, and change from baseline in anti-GCase antibody isotypes and titers.

In case of presence/increase of anti-GCase antibodies, any investigation of the presence of neutralizing anti-GCase antibodies, as well as the clinical relevance of their presence with regards to (i) reduction of enzyme activity in blood, plasma and cells; (ii) reduction in transduced progenitor cells and VCN; (iii) autoimmune-mediated cytopenias will be discussed in the CSR.

9.3.4. BMD

Observed values and absolute change from baseline in BMD values assessed by DXA will be listed.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided.

9.3.5. Chitotriosidase Enzyme Activity in Plasma

Observed values and absolute change from baseline in chitotriosidase enzyme activity level values in plasma will be listed. Any values >38.1 µmol/L/h will be flagged on the listing.

Figures displaying individual values over time, with study week on the x-axis will also be provided.

A horizontal reference line will be added at the ULN of 38.1 µmol/L/h.

Dashed horizontal reference line will be added at the LLQ of 0.8 µmol/L/h and at the ULQ of 150 µmol/L/h. Any values at or above ULQ will not be included on the figure and a footnote will describe their exclusion.

9.3.6. BMB

Observed values and absolute change from baseline in BMB score assessed by bone MRI will be listed.

Figures displaying individual values over time, with study week on the x-axis, along with arithmetic or geometric means, will also be provided.

9.4. Exploratory Efficacy Analyses

9.4.1. SF-36

Observed values and absolute change from baseline in the eight SF-36 subscale scores (i.e., Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning, and Mental Health) and 2 component summary scores (Physical Functioning and Mental Functioning) will be listed.

9.4.2. BPI-SF

Observed values and absolute change from baseline in BPI-SF questionnaire scores for pain severity and pain interference will be listed.

9.4.3. Exploratory biomarkers for Gaucher disease in serum, plasma, urine, and whole blood derived leukocytes, or subpopulations

Observed values and absolute change from baseline in exploratory biomarkers for Gaucher disease in serum, plasma, urine, and whole blood derived leukocytes, or subpopulations will be listed.

9.4.4. Exploratory genomic biomarkers for Gaucher disease in whole blood at Screening (ie, CHIT1, gene encoding chitotriosidase)

As knowledge of Type 1 Gaucher disease pathophysiology and related biomarkers continues to evolve, back-up plasma and urine samples will be collected and archived for possible future non-genomic and genomic biomarker testing either at specialized laboratories or a Biorepository site. These samples will be destroyed 5 years after the CSR is finalized.

9.4.5. Average VCN and ISA results in Whole Blood and Bone Marrow

Average VCN and ISA results in whole blood and bone marrow will be listed.

For subjects with an average VCN in PBLs ≥ 0.01 as determined by the central laboratory, suggesting $\geq 1\%$ of the sampled blood cells are vector-positive with an average of 1 copy/diploid genome (c/dg), testing for vector ISA will also take place.

10. SAFETY ANALYSES

All safety analyses will be conducted on the Safety and Infused populations.

No inferential statistical testing will be performed for safety variables.

10.1. Primary Safety Analysis

10.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the IMP. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the IMP, regardless of whether the event is causally related to the IMP.

The definition of an AE also covers:

- Medication errors and uses outside what is foreseen in the protocol, including accidental overdose, if an AE results from the error;
- Any Grade 3 or higher platelet count, grade 3 or higher WBC count, and grade 2 or higher neutrophil count (grade determined by CTCAE) regardless of whether considered clinically significant by Investigator report;
- Fertility-related events, considered an AE of special interest (AESI) for the study.

Adverse events will be coded using MedDRA® version 23.0.

10.1.1.1. Treatment-emergent Adverse Events

Any AE that started prior to mobilization with G-CSF is considered a pre-treatment AE and is listed, but not included in tabulations (except for tabulations using study periods where Pre-Mobilization is included). However, pre-treatment AEs that worsen/increase in severity after the subject started mobilization with G-CSF will be recorded as new AEs and consequently will be regarded as treatment emergent and thus will be included in the tabulations.

10.1.1.2. Serious Adverse Events

An SAE is any untoward medical occurrence or effect that:

- Results in death
- Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- Results of in-patient hospitalisation or a prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see below)
- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions
- Results in congenital anomaly/birth defect in the offspring of a subject who received AVR-RD-02
- Is an important medical event that may not result in death, be life threatening, or require

hospitalisation, but that, based upon appropriate medical judgment, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed in Protocol
- Causality of the SAE(s)
- Outcome of the SAE(s)
- Redacted medical records and laboratory/diagnostic information.

10.1.1.3. Adverse Drug Reaction or Adverse Reaction

All untoward and unintended responses to an investigational medicinal product. The phrase responses to an investigational medicinal product means that a causal relationship between the investigational medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.1.1.4. Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unauthorized AVR-RD-02 or summary of product characteristics for an authorized product).

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Investigator's Brochure and that are identified as related to study treatment.

10.1.1.5. Adverse Event Severity

AE severity will be graded using the CTCAE v4.03. The CTCAE is a descriptive terminology utilized for AE reporting. A grading (severity) scale is provided for each AE term.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5, with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- **Grade 3** Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.
    - Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Change in severity of an AE should be documented based on specific guidelines in the eCRF completion guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

10.1.1.6. Adverse Event Relationship

The relationship between an AE and AVR-RD-02, mobilization (G-CSF or plerixafor), apheresis, conditioning (busulfan), anti-convulsant medication(s), study procedures or underlying disease will be assessed based on clinical experience and classified according to the following:

- Definite
  - Event or laboratory test abnormality, with plausible time relationship to drug intake
  - Cannot be explained by disease or other drugs
  - Response to withdrawal plausible (pharmacologically, pathologically)
  - Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
  - Rechallenge satisfactory, if necessary
- Probable
  - Event or laboratory test abnormality, with reasonable time relationship to drug intake
  - Unlikely to be attributed to disease or other drugs
  - Response to withdrawal clinically reasonable
  - Rechallenge not required
- Possible
  - Event or laboratory test abnormality, with reasonable time relationship to drug intake
  - Could also be explained by disease or other drugs
  - Information on drug withdrawal may be lacking or unclear
- Unlikely
  - Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
  - Disease or other drugs provide plausible explanations
- Unrelated
  - Event or laboratory test abnormality is plausibly related to the subject's clinical state, underlying disease, or the study procedure/conditions
  - Time relationship to drug intake makes a relationship unreasonable
  - Other obvious causes for event or laboratory test abnormality exist
- Unknown
  - Report suggests an AE; however, cannot be judged at this time because information is insufficient or contradictory

    - More data for proper assessment is needed, or additional data is under examination
- Not applicable (N/A)
    - Report suggests an AE; however, the need to assess causality is not practical or of value, due to the event itself, or to the circumstances surrounding the event

Adverse events classified as "Not applicable" will not be included in tabulations.

10.1.1.7. Adverse Event Outcome

Investigators will be instructed to report to the Sponsor or its designee their assessment of the outcome of each AE (both serious and non-serious). Definitions for possible AE outcomes include:

- Recovered/Resolved: the event has improved or the patient recuperated;
- Recovered/Resolved with Sequelae: the patient recuperated but retained pathological conditions directly resulting from the disease or injury;
- Recovering/Resolving: the event is improving;
- Not Recovered/Not Resolved: the event has not improved or the patient has not recuperated;
- Fatal: termination of life as a result of an AE. There should be only one AE marked with this outcome;
- Unknown: not known, not observed, not recorded, or refused.

10.1.1.8. Adverse Event Tabulations

All AEs (serious and non-serious) occurring after completion of the informed consent process and before the end of study will be included and classified by system organ class (SOC) and preferred term (PT) using MedDRA® v23.0. Date imputation algorithm from Section 5.7.15 will be employed to partial dates.

A data listing of all AEs, including pre-treatment AEs (as defined in Section 5.7.15), will be provided including verbatim term, SOC, PT, toxicity, relationship to mobilization (G-CSF or plerixafor), relationship to apheresis, relationship to conditioning, relationship to AVR-RD-02, relationship to study procedure, relationship to underlying disease, date/time and day of onset, date/time and day of resolution, duration, possible co-medication, treatment given to treat the adverse event, the outcome, whether the event was an SAE, and whether it led to withdrawal. The derived study onset period used to tabulate AEs by onset will also be included. AEs prior to G-CSF for Mobilization will be flagged on this listing. In addition, a separate listing of all serious AEs will be provided, with any SAEs prior to treatment (Mobilization) flagged.

Deaths, if any, will be listed for subject, date/time, primary cause and autopsy finding.

Listings will be sorted by subject identification number, onset date/time, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day then partial dates for AEs will be imputed as per Table 3 to allow AEs to be sorted appropriately. Imputed dates will not be listed.

The AE tabulations, unless stated otherwise, will be based on TEAEs. Therefore, all pre-treatment AEs will be excluded from the tabulations, unless stated otherwise. However, pre-treatment AEs that worsen/increase in severity after G-CSF for Mobilization will be recorded as new AEs and consequently will be regarded as treatment emergent and thus will be included in the tabulations.

Descriptive statistical methods will be used to tabulate the TEAE data including both the number of subjects and number of events. TEAE tables including the number of events will be presented in the following order: number of subjects, (percentage of subjects) and [number of events].

TEAEs will be presented in descending order of frequency across all subjects.

When it is necessary to calculate percentages, the denominator will be the total number of subjects in the analysis population, unless otherwise stated, and the numerator will be the total number of subjects reporting a TEAE within the relevant category. For AEs by Onset, the denominator used for each study period will be the number of subjects who participated in the study period. For AEs by Causal Relationship, the denominator used will only include evaluable subjects (e.g., a subject can only be included in the Busulfan category if they underwent conditioning with busulfan).

For tabulations by SOC and PT, when tabulating the number of subjects, if a subject has repeated episodes of a particular TEAE, all episodes will be counted in the tabulation, however, a subject with multiple events will only be counted once within each SOC and PT. A subject with more than one type of AE in a particular SOC will be counted only once in the total of subjects experiencing AEs in that particular SOC. Since a subject could have more than one type of AE within a particular SOC, the sum of subjects experiencing different AEs within the SOC could appear larger than the total number of subjects experiencing AEs in that SOC. Similarly, a subject who has experienced an AE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs. Furthermore, SOC and PT will be presented in descending order of frequency (i.e., order by the overall grouping in descending frequency for each SOC and also for each PT within each SOC; in each case where there are equal frequencies items would be ordered alphabetically).

For tabulations by severity, the maximum severity for each subject will be used. A missing severity will not be imputed, but a row labelled ‘Missing’ will be included. If a subject has multiple events with the same SOC or PT, they will be counted under the worst severity for the tabulation, but the events will be counted under the applicable severity category.

If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship, will be counted in the tabulations.

Plots of cumulative AE counts over time will be produced, with study day on the x-axis presented relative to date of AVR-RD-02 infusion (Study Day 1) for the Infused Population and relative to date of (first) signing of ICF for the Safety Population. When using the Infused Population, vertical reference lines will be included to represent the study day the subjects received their AVR-RD-02 infusion and their first and last doses of busulfan. These cumulative AE plots will be repeated for AEs ≥ Grade 3, and for AEs that are deemed possibly, probably or definitely related to busulfan. Where a single AE is captured multiple times due to changing severity, each change in Grade will contribute to the cumulative number of AEs for that subject.

If it is possible to identify such AEs, the plots will be repeated with the multiple events collapsed into a single AE occurrence (with the causality and maximum grade considered appropriately).

- **Overall Summary of TEAEs**

The summary will include number of subjects (percentage of subjects) [number of events] for subjects with:

- At least one TEAE
- TEAEs related* to G-CSF for Mobilization
- TEAEs related to Plerixafor
- TEAEs related to Apheresis
- TEAEs related to Anti-Convulsant
- TEAEs related to Busulfan
- TEAEs related to Auxiliary Medication(s) or associated procedure
    - Combine G-CSF for Mobilization, Plerixafor, Apheresis, Anti-Convulsant and Busulfan
- TEAEs related to AVR-RD-02 infusion
- TEAEs related to Study Procedures
- TEAEs related to Underlying Disease
- TEAEs leading to Withdrawal
- TEAEs leading to Discontinuation of the Study
- TEAEs leading to Death
- Each CTCAE Grade
- Any severe (CTCAE Grade ≥ 3) TEAE
- Maximum CTCAE Grade
- At least one Treatment-Emergent SAE (TESAE)

  * 'related' includes those with a deemed possible, probable or definite causal relationship

- **AEs by Onset**

AEs by SOC and PT will be tabulated using the onset date/time of each adverse event to assign each AE into a study period according to Section 5.7.15. The summary will include number of subjects (percentage of subjects) [number of events]. Note since Pre-Mobilization is included that these tabulations include all AEs as well as TEAEs, and the denominator used to calculate percentages will be the number of subjects who participated in the study period:

- Pre-Mobilization: started before first dosing of G-CSF for Mobilization
- Auxiliary Medications:
    - Mobilization:
        - G-CSF: started (or worsened) on or after first dosing of G-CSF for Mobilization and before start of apheresis

        - For any subject who received Mobilization twice, the study period between the start of the second Mobilization until the start of the second apheresis will be captured as Mobilization #2
    - Apheresis:
        - started (or worsened) on or after start of apheresis until the end of the last apheresis
        - For any subject who received apheresis twice, the study period between the start of the second apheresis until the end of the second apheresis will be captured as Apheresis #2
    - Post-Apheresis: started (or worsened) after the end of the last apheresis and before first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan
        - For any subject who received Mobilization twice, the study period between the end of the first apheresis and the start of Mobilization #2 will be captured as Post-Apheresis
            - The study period between the end of the second apheresis and the first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan will be captured as Post-Apheresis #2
        - For any subject, who received Mobilization but did not proceed to receive conditioning or AVR-RD-02, the study period after the end of Apheresis will be captured as Post-Apheresis
    - Conditioning: started (or worsened) on or after first dosing of anti-convulsant medication given for prophylaxis ahead of busulfan and before date of AVR-RD-02 infusion
- AVR-RD-02 Infusion: started (or worsened) on or after the start of infusion of AVR-RD-02
- Post-AVR-RD-02 Infusion Follow-Up: started (or worsened) after the end of AVR-RD-02 infusion

- **Serious Adverse Events**

SAEs will be listed.

- **TEAEs by SOC, PT and CTCAE Grade**

A tabulation of TEAEs by SOC and PT will be presented for each CTCAE Grade 1 to 5, Grade ≥2 and ≥Grade 3. The column for ≥Grade 3 will be used to determine decreasing order of frequencies. The summary will include number of subjects (percentage of subjects) [number of events].

- **AEs by Causal Relationship**

AEs by Onset will be repeated using the deemed causal relationship (possible, probable or definite) to each auxiliary medication (G-CSF, plerixafor, busulfan, anti-convulsant), apheresis,

AVR-RD-02, or study procedure, in turn. The summary will include number of subjects (percentage of subjects) [number of events]. Note since Pre-Mobilization is included that these tabulations include all AEs as well as TEAEs, and the denominator used to calculate percentages will be the number of subjects who participated in the study period.

10.1.1. Presence of Replication Competent Lentivirus (RCL)

Results of the peripheral blood tests will be listed, with absence of RCL identified by a negative result. In case of confirmed positivity, any resulting RCL culture test results will be listed.

10.1.2. Identification of mononuclear cells with integration site profiles suggestive of aberrant clonal expansion(s)

Monitoring for aberrant clonal expansion (ACE) requires the clinical review of multiple datasets (e.g., routine clinical and laboratory surveillance, repertoire study, bone marrow examination, integration site analysis). Therefore, no summary tables focused solely on ACE will be produced. The results of the manual clinical review for ACE will be described in the summary documents with cross-reference to the relevant study listings and a separate integration site analysis report.

10.1.3. Clinical Laboratory Evaluations

The details of measurement of laboratory parameters are described in the study protocol. International System (SI) units will be used in all outputs.

Serum chemistry includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), amylase, lipase, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, calcium, albumin, phosphate, magnesium, uric acid, and glucose.

Electrolytes include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), and serum creatinine.

Hematology includes hematocrit, hemoglobin, platelet count, WBC count (total and differential), RBC count, and ANC.

All hematology, serum chemistry and urinalysis data including CFB will be listed. In these listings, sample collection data (e.g., collection times) for laboratory analysis and urinalysis data will be included, and individual data will be flagged with an “H” or an “L” for values that are higher or lower than their normal ranges, respectively, and any clinically significant (CS) and not clinically significant (NCS) records will be flagged.

For the listings of ALT and of AST, the following values will be flagged to indicate evidence of Drug-Induced Liver Injury:

- ALT or AST > 8×ULN
- ALT or AST > 5×ULN
    - In the CSR, an assessment will be made of whether ALT or AST remained above 5×ULN for more than 2 weeks
- ALT or AST > 3×ULN

- In the CSR, an assessment will be made of whether ALT or AST remained above 3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For the listing of ANC values, a flag will indicate ANC < 0.5 (10^9/L).

For the listing of platelet values, flags will indicate platelets < 35 (10^9/L) and < 20 (10^9/L).

For each laboratory parameter with a defined normal range, absolute values will be defined at each protocol-scheduled time point as low, normal, or high, and post-baseline values will be compared to the baseline value through shift tables.

In addition, one flag will be derived to identify whether the parameter had at least one value above the normal range at any time post-treatment, and another to identify whether the parameter had at least one value below the normal range at any time post-treatment. Subjects having both High and Low values relative to normal ranges at post-treatment visits for laboratory parameters will be counted in both the High and Low categories of the "Any visit post-treatment" row of related summary tables.

The denominator used in laboratory shift table summaries will only include evaluable subjects (i.e., those who have both a baseline and at least one post-baseline value recorded).

Individual subject data for the ratio of value to LLN for Hgb, HCT, ANC, Platelets, Reticulocytes and Leukocytes will be plotted vs. study week, with a line for each parameter on the same plot and one plot for each subject. Vertical reference lines will be included to represent the study day the subjects received their AVR-RD-02 infusion and their first and last doses of busulfan. A horizontal reference line will be included at 1.

Any available microscopic urinalysis will also be listed.

Partial thromboplastin time (PTT) and international normalized ratio (INR) will be listed.

Flow cytometric analysis of T and B cell counts as well as peripheral blood lymphocyte subsets (CD3, CD4, CD8, CD19, and CD16/56) will be listed.

10.1.1. Achievement of Hematological Engraftment

The occurrence of hematological reconstitution is defined as the first day of absolute neutrophil count (ANC) ≥ 0.5 (10^9/L) and of platelets ≥ 20 (10^9/L) (in the absence of platelet transfusions), i.e. time (days) from date of AVR-RD-02 infusion to the first date of the three consecutive values.

For the Infused Population, panel plots of individual subjects will be presented for ANC (10^9/L) between study day -50 and study day 100, with study day on the x-axis. Vertical reference lines will be included at study day 1 (solid, black), 35 (dashed, red), 42 (solid, red) and 49 (dashed, red) and to represent the study day the subjects received their AVR-RD-02 infusion and their first and last doses of busulfan. A horizontal reference line will be included at 0.5 (10^9/L). On the x-axis, red arrows will indicate the study days that G-CSF was administered.

For the Infused Population, panel plots of individual subjects will be presented for platelet counts (10^9/L) between study day -50 and study day 100, with study day on the x-axis. Vertical reference lines will be included at study day 1 (solid, black), 35 (dashed, red), 42 (solid, red) and

49 (dashed, red) and to represent the study day the subjects received their AVR-RD-02 infusion and their first and last doses of busulfan. Horizontal reference lines will be included at 20 and 35 (10^9/L). On the x-axis, red arrows will indicate the study days that any platelet transfusions were administered.

10.1.2. Rescue Medication

To ensure subject safety, a CD34+ stem cell back-up of non-transduced cells will be collected and stored for use as rescue treatment in the unlikely event that there is prolonged bone marrow aplasia after AVR-RD-02 treatment.

Any such cases of rescue treatment will be listed.

10.1.3. Vital Signs Evaluations

All individual vital signs results (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature), including vital signs taken prior to apheresis, and pre-infusion (window -10 minutes) and post-infusion (window +10 minutes) on the day of AVR-RD-02 infusion, will be presented in data listings. Any potentially clinically significant (PCS) values will be flagged, where PCS are defined as follows:

	PCS – Low if:			PCS – High if:		
	Observed Value is:	AND	Decrease from Baseline is:	Observed Value is:	AND	Increase from Baseline is:
Systolic Blood Pressure	<90 mmHg		≥20 mmHg	>180 mmHg		≥20 mmHg
Diastolic Blood Pressure	<50 mmHg		≥10 mmHg	>105 mmHg		≥10 mmHg
Heart Rate	<50 bpm		≥15 bpm	>120 bpm		≥15 bpm

10.1.4. ECG Evaluations

All individual ECG parameter results (heart rate, PR interval, RR interval, QRS interval, QT interval, QT interval corrected using Bazett's formula (QTcB) and Fridericia's formula (QTcF)) and the clinical assessment of the ECG will be presented in data listings. Any potentially clinically significant (PCS) values will be flagged, where PCS are defined as follows:

- QTcF Interval (ms) and increase from baseline in QTcF Interval (ms)
  - > 450 and increase > 30
  - > 500 and increase > 60

- PR > 200 msec and >25% increase from baseline
- QRS > 100 msec and >25% increase from baseline

10.1.5. Physical Examination

Physical examination data will be listed.

10.1.6. Pregnancies

Cases of pregnancy that occur in female subjects or partners of male subjects during exposure to study treatment are to be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Pregnancy data collected during this study for all subjects will be listed.

10.2. Exploratory Safety Analysis

10.2.1. Reproductive Potential

Reproductive potential for male subjects will be evaluated based on sperm count, volume, sperm concentration, total motility, progressive motility, and morphology.

Reproductive potential for female subjects will be evaluated based on changes in menstrual history monthly and in ovarian reserve as assessed by anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

All individual results and CFB will be presented in data listings. Values outside the laboratory reference range will be flagged (low-L, high-H).

10.3. Other Safety Measures

Any other safety data will be listed only.

10.4. Changes to Planned Analyses

The SAP has been written in consideration of an Abbreviated CSR.

The analysis sets in the protocol have been replaced by the All Subjects, Safety, and Infused Populations.

Any 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.

If any modifications in the experimental design, dosages, parameters, subject selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

11. REFERENCES

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