1 TITLE PAGE

Statistical Analysis Plan

(Methods)

Protocol Number CTX001-121, Version 6.11

A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects with Severe Sickle Cell Disease

[redacted]

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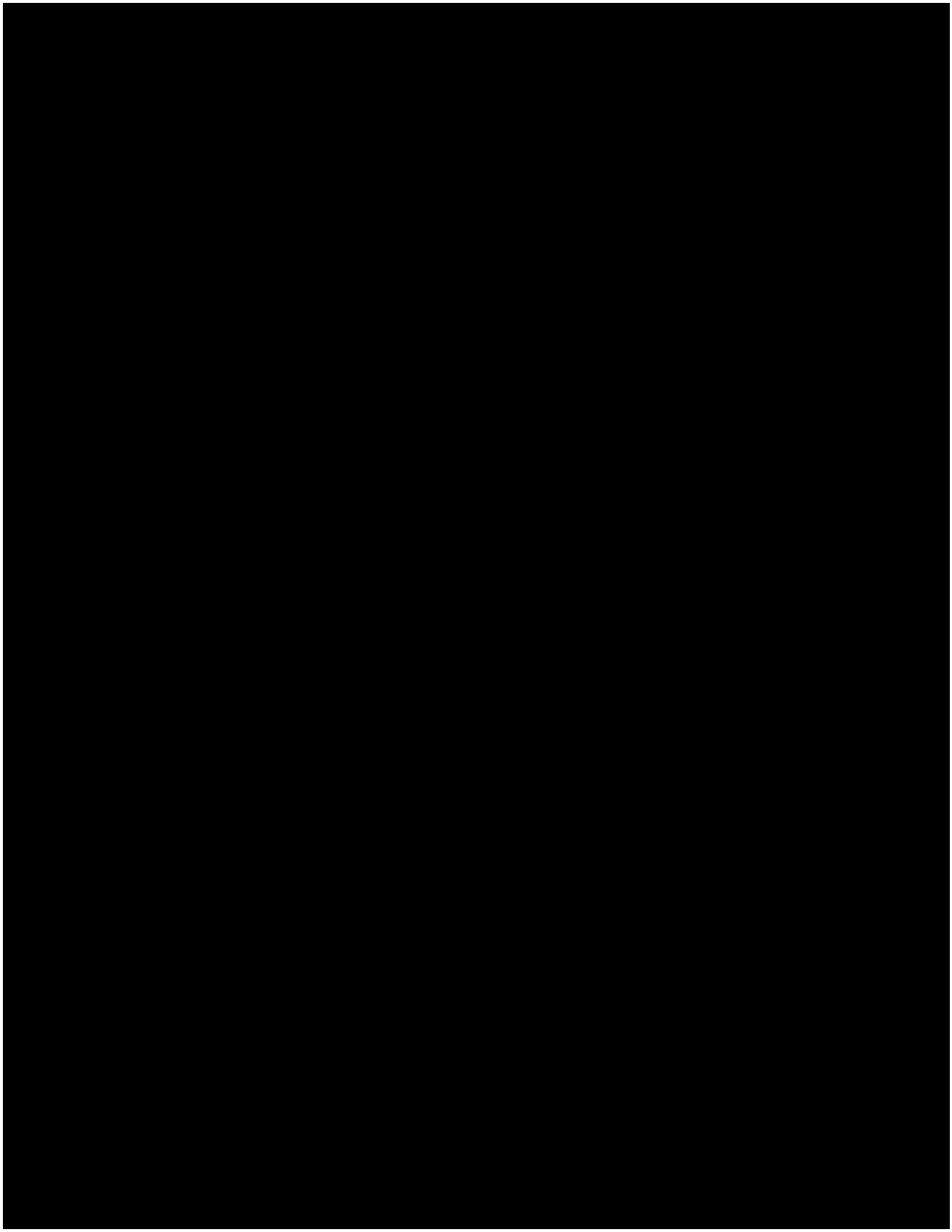
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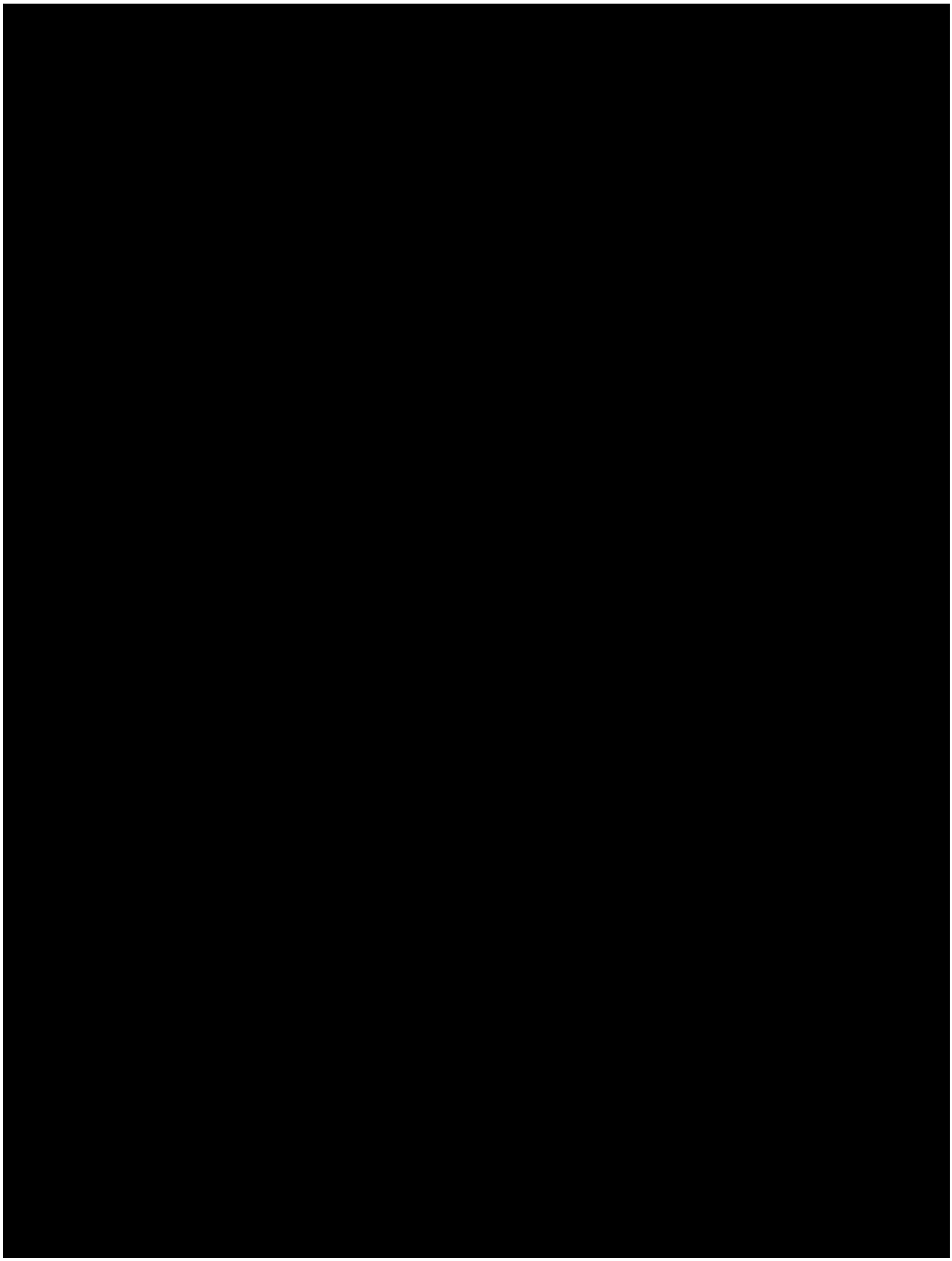
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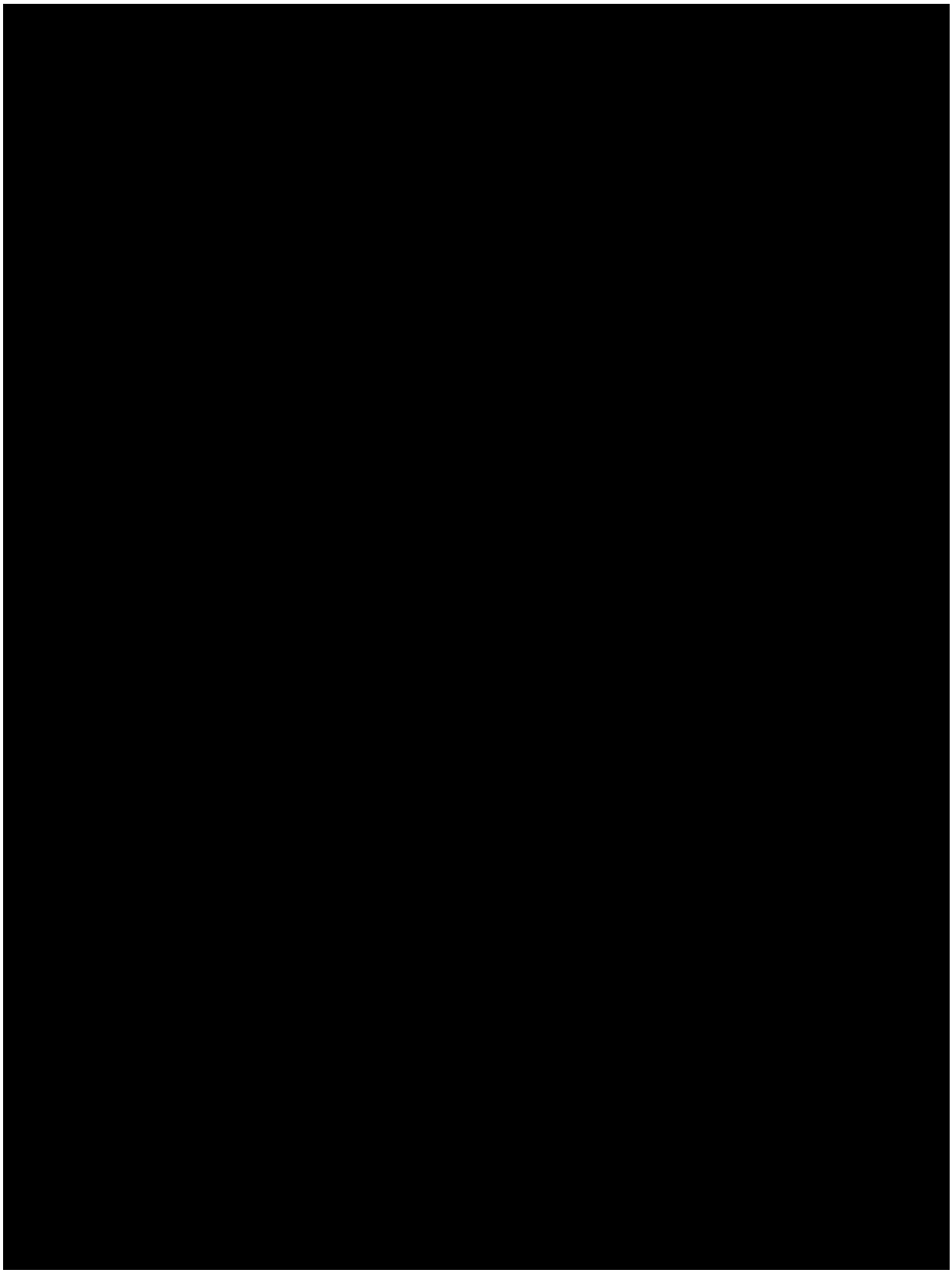
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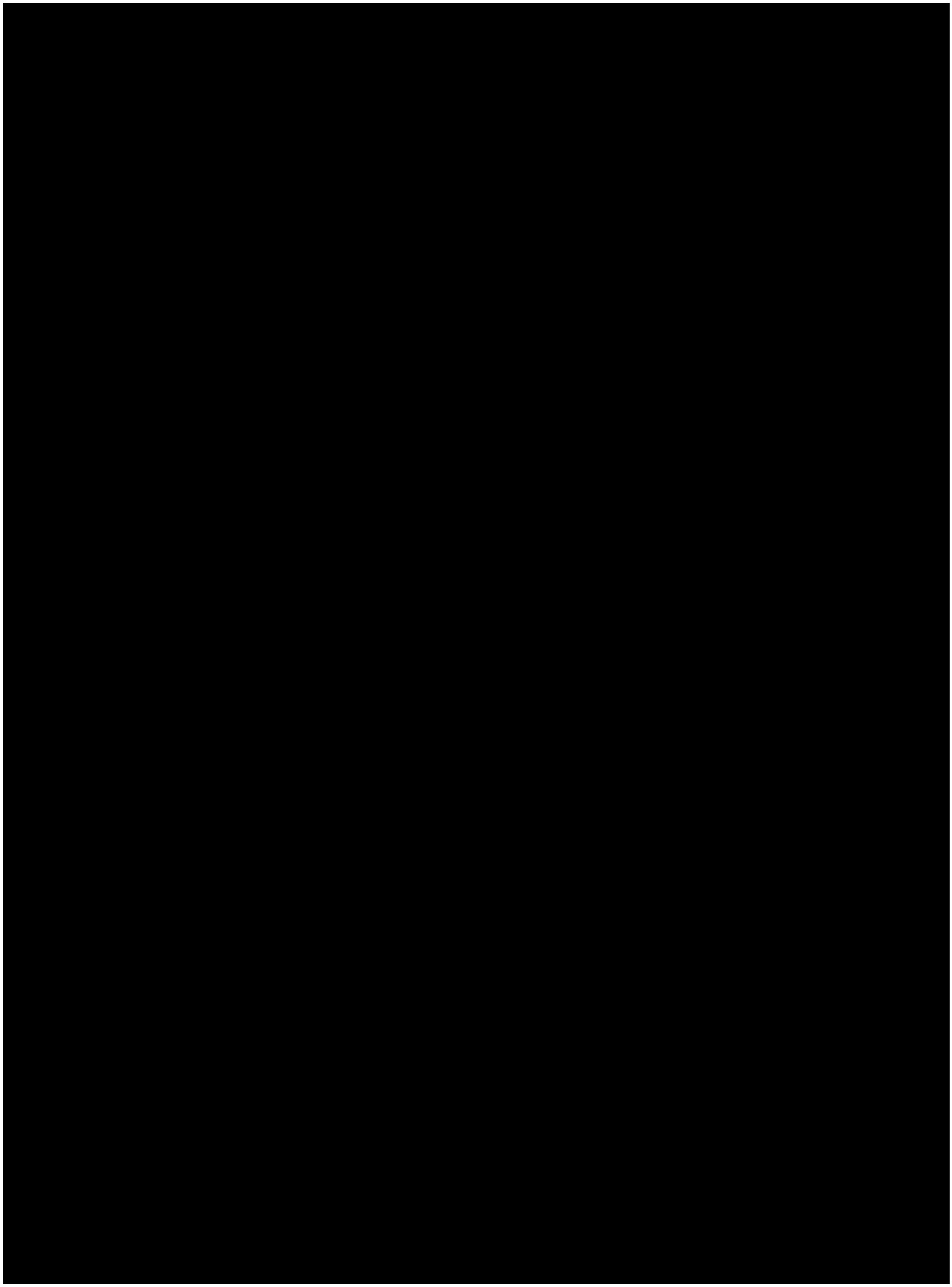
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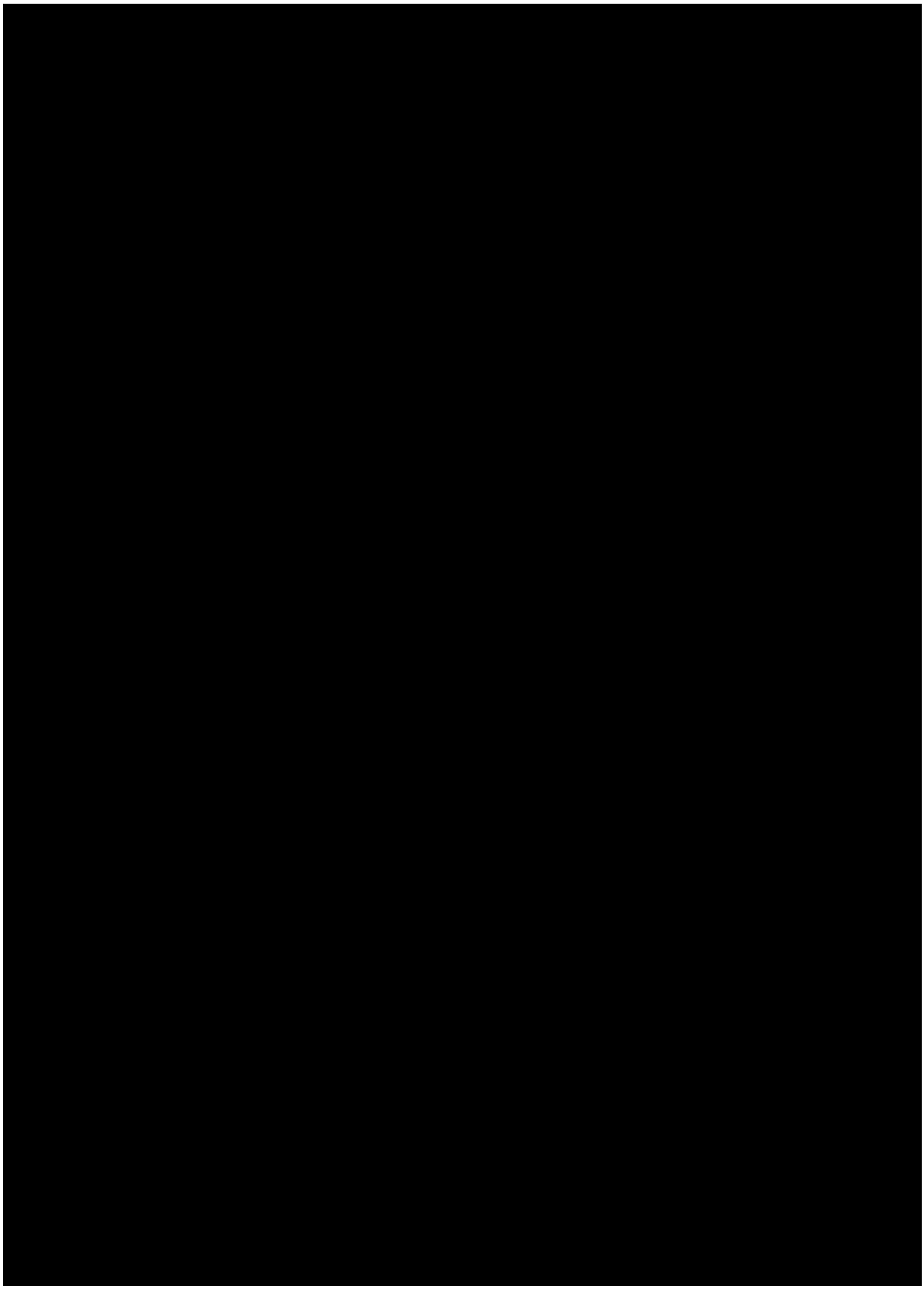
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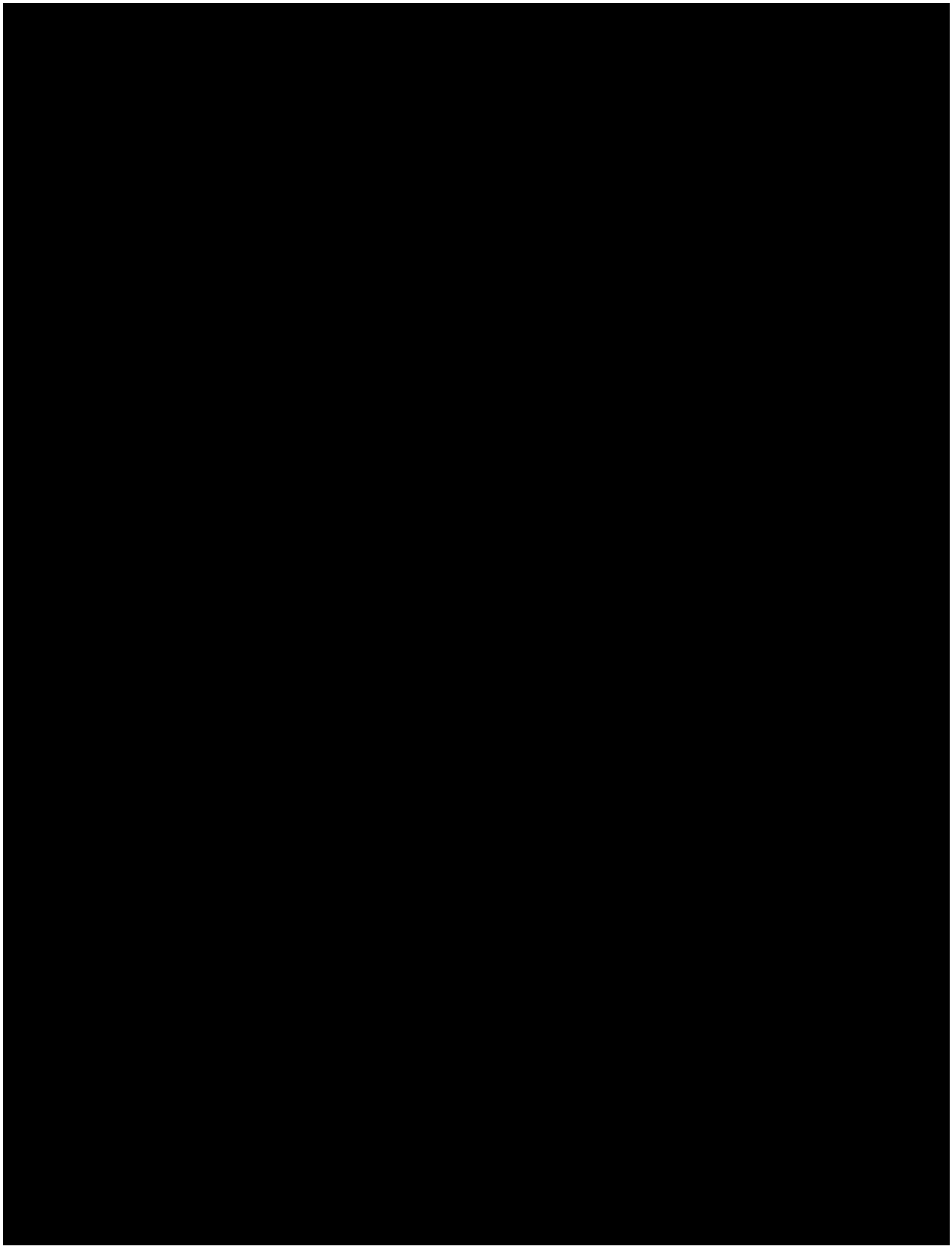














4 INTRODUCTION

This SAP, which describes the planned interim analyses and the final analysis for Study CTX001-121, is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), the most recent approved eCRF completion guidelines, and the most recent approved endpoint adjudication committee charter.

Study CTX001-121 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study of the safety and efficacy of autologous CRISPR-Cas9 modified $CD34^+$ human hematopoietic stem and progenitor cells (CTX001) in subjects with severe sickle cell disease (SCD). The total sample size is approximately 45 subjects.

This SAP documents the planned interim and the final statistical analysis of efficacy and safety endpoints in the CTX001-121 study protocol. Unless specified otherwise, analyses of exploratory endpoints specified in the study protocol, will be described in the exploratory analysis plan and hence be outside of the scope of this SAP.

The Vertex Biometrics Department will perform the statistical analysis of the efficacy and safety data; SAS® (Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings and datasets). The first version of SAP was finalized and approved prior to the infusion of CTX001 to the first subject. The current version of SAP will be finalized before the first interim analysis for US submission.

5 STUDY OBJECTIVES

5.1 Primary Objective

- Evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified $CD34^+$ human hematopoietic stem and progenitor cells (hHSPCs) (CTX001) in subjects with severe SCD.

5.2 Secondary Objectives

The secondary objectives of the study are as follows:

- Assess the effects of infusion of CTX001 on disease-specific events and clinical status.
- Quantify gene editing efficiency.

5.3 Exploratory Objective

- Assess the ability of biomarkers to characterize CTX001 effect and predict treatment outcomes.

6 STUDY ENDPOINTS

6.1 Safety Endpoints

- Successful neutrophil engraftment within 42 days after CTX001 infusion (Study Day 43).

- Time to neutrophil engraftment.
- Time to platelet engraftment.
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, and vital signs.
- Transplant-related mortality (TRM) within 100 days and within 12 months post-CTX001 infusion.
- All-cause mortality.

6.2 Efficacy Endpoints

6.2.1 Primary Efficacy Endpoint

- Proportion of subjects who have not experienced any severe VOC for at least 12 consecutive months (VF12) after CTX001 infusion. The evaluation of VF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management.

6.2.2 Key Secondary Efficacy Endpoint

- Proportion of subjects free from inpatient hospitalization for severe VOCs sustained for at least 12 months (HF12) after CTX001 infusion. The evaluation of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management.
- Proportion of subjects who have not experienced any severe VOC for at least 9 consecutive months (VF9) any time after CTX001 infusion. The evaluation of VF9 starts 60 days after last RBC transfusion for post-transplant support or SCD disease management.

6.2.3 Secondary Efficacy Endpoints

- Achieving at least 90%, 80%, 75%, 50% reduction from baseline in annualized rate of severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved VF12.
- Relative reduction from baseline in annualized rate of severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved VF12.
- Duration of severe VOC free in subjects who have achieved VF12.
- Relative reduction from baseline in annualized rate of inpatient hospitalization for severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved HF12.

- Relative reduction from baseline in annualized duration of hospitalization for severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved HF12.
- Proportion of subjects with sustained HbF ≥20% at the time of analysis for at least 3 months, 6 months, or 12 months. The evaluation starts 60 days after last RBC transfusion for post-transplant support or SCD management.
- Relative reduction from baseline in number of units of red blood cells (RBC) transfused for SCD-related indications up to 24 months starting after Month 12 post CTX001 infusion.
- HbF concentrations (in absolute value and %) over time.
- Hemoglobin (Hb) concentrations over time.
- Change from baseline in reticulocyte count (in absolute and %) over time.
- Change from baseline in indirect bilirubin over time.
- Change from baseline in haptoglobin over time.
- Change from baseline in lactate dehydrogenase (LDH) over time.
- Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time.
- Proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow over time.
- Change in patient reported outcomes (PROs) over time in adults (≥18 years of age) using
    - Pain-scale:11-point numerical rating scale (NRS)
    - Functional assessment of cancer therapy bone marrow transplant (FACT-BMT)
    - Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me)
    - EuroQol Quality of Life Scale (EQ5D5L)
- Change in PROs over time in adolescents (12 to <18 years of age) using
    - Pain-scale:11-point NRS
    - Pediatric Quality of Life Inventory (PedsQL Teen self-report and parent proxy versions)
    - PedsQL SCD module (Teen self-report and parent proxy versions)
    - EQ-5D-Youth (EQ-5D-Y self-report and parent proxy version)

6.3 Exploratory Endpoints

- Change in tricuspid regurgitant jet velocity (TRV) over time.

- Change in proportion of circulating erythrocytes expressing fetal hemoglobin (F-cells) over time.
- Change in inflammatory and endothelial activation markers over time.
- Change in urine albumin to creatinine ratio (UCAR) over time.

Unless specified otherwise, the analysis of exploratory endpoints will be described in the exploratory analysis plan and hence be outside of the scope of this SAP.

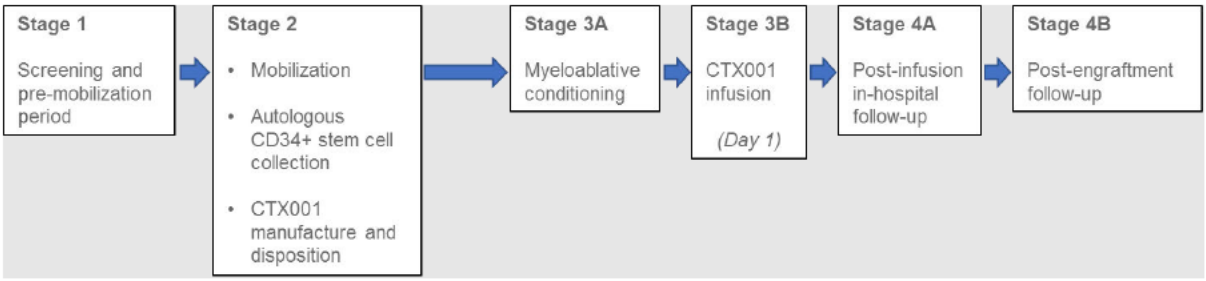
7 STUDY DESIGN

7.1 Overview of Study Design

This is a single-arm, open-label, multisite, single dose, Phase 1/2/3 study that will enroll subjects with severe SCD.

A schematic of the study design is provided in Figure 7-1.

Figure 7-1 CTX001-121 Study Design



This study includes the following stages:

- Screening and pre-mobilization (Stage 1): approximately 2 to 4 months
- Mobilization, autologous $CD34^+$ stem cell collection, CTX001 manufacture and disposition (Stage 2): approximately 2 to 4 months
- Myeloablative conditioning and infusion of CTX001 (Stage 3): approximately 1 month
- Follow-up through engraftment and up to 2 years after CTX001 infusion (Stage 4): approximately 2 years

The study will initially enroll up to 17 subjects to provide a preliminary evaluation of safety and efficacy of CTX001. The study may be expanded to include a total of up to approximately 45 dosed subjects. Additionally, all subjects infused with CTX001 product will be asked to enroll to a long-term follow-up study (Study VX18-CTX001-131) following completion or withdrawal/ discontinuation.

7.2 Sample Size and Power

With a total of 45 subjects dosed, 3 interim analyses (IAs) may be performed following a group sequential testing procedure in the expanded study to allow for early evaluation of efficacy. Details of the interim analyses are described in Section 9.3.4 and Section 10.1. This sample size will provide at least 95% power to rule out a response rate of 50% when the true

response rate is 80% for both the primary and key secondary efficacy endpoints with one-sided alpha of 2.5%. The operating characteristics under different scenarios of the true response rate for the primary and key secondary efficacy endpoints are shown in Table 7-1.

Table 7-1 Operating Characteristics of Efficacy Boundaries for Primary and key Secondary Efficacy Endpoints

Analysis Stage	Efficacy Boundary	Boundary in Response Rate (95% CI)	Probability of Crossing Efficacy Boundaries Under Different Response Rates (p_1) [a]		
			p_1 =80%	p_1 =85%	p_1 =90%
IA1: N=10	9/10	90.0% (55.5%, 99.7%)	37.6%	54.4%	73.6%
IA 2: N=17	14/17	82.4% (56.6%, 96.2%)	54.9%	75.6%	91.7%
IA 3: N=30	22/30	73.3% (54.1%, 87.7%)	87.1%	97.2%	99.8%
Final: N=45	31/45	68.9% (53.4%, 81.8%)	97.5%	99.8%	>99.9%
Overall Power			97.9%	99.9%	>99.9%

a: Marginal probability of crossing the efficacy boundary at a specific interim analysis or final analysis.

7.3 Randomization

This is a single-arm, single-dose study.

7.4 Blinding and Unblinding

This is an open-label study.

8 ANALYSIS SETS

The following analysis sets are defined: Enrolled Set, Safety Analysis Set, Full Analysis Set, Primary Efficacy Set, and Early Efficacy Set.

8.1 Enrolled Set

The **Enrolled Set** includes all enrolled subjects who have signed informed consent and met the eligibility criteria. Listing of the demographics and baseline characteristics will be provided based on the Enrolled Set.

8.2 Safety Analysis Set

The **Safety Analysis Set** is a subset of the Enrolled Set that includes subjects who have started the mobilization regimen.

8.3 Full Analysis Set

The **Full Analysis Set** (FAS) is a subset of the Enrolled Set that includes subjects who had received CTX001 infusion. The demographics and baseline characteristics will be summarized based on FAS.

8.4 Primary Efficacy Set

The **Primary Efficacy Set** (PES) is a subset of FAS that includes all subjects who have been followed for at least 16 months post CTX001 infusion and for at least 14 months after completion the RBC transfusions for post-transplant support or SCD management. Completion of the (initial) RBC transfusions is determined when all those transfusions for post-transplant support or SCD management have finished followed by 60 days without transfusion. Subjects who complete the 24 months of follow-up in the study post CTX001 infusion will be included in this set. In addition, subjects who die or discontinue the study due to CTX001-related adverse events and have less than 16 months follow-up post CTX001 infusion, or continuously receive RBC transfusions for more than 10 months post CTX001 infusion will also be included in this set.

8.5 Early Efficacy Set

The **Early Efficacy Set** is a subset of FAS that includes all subjects who have been followed for at least 12 months post CTX001 infusion and for at least 11 months after completion the RBC transfusions for post-transplant support or SCD management. Completion of the (initial) RBC transfusions is determined when all those transfusions for post-transplant support or SCD management have finished followed by 60 days without transfusion. Subjects who complete the 24 months of follow-up in the study post CTX001 infusion will be included in this set. In addition, subjects who die or discontinue the study within 12 months follow-up post CTX001 infusion due to CTX001-related adverse events, or continuously receive RBC transfusions for more than 13 months post CTX001 infusion will also be included in this set.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix A. All data will be listed by individual subject. The precision standards for reporting safety and efficacy variables are provided in a Vertex Biometrics document that specifies the programming rules including the precision for derived variables.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). For certain continuous variables, such as HbF, additional summary statistics including the 1st and the 3rd quartiles will also be presented.

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before start of mobilization.

For numbers of severe VOCs, all pre- and post-CTX001 infusion severe VOCs will be adjudicated by an endpoint adjudication committee (EAC) to determine whether they meet the protocol criteria for severe VOCs. Baseline will be calculated using records of all severe VOCs adjudicated by the EAC as meeting the protocol definition of severe VOC, during the 2 years prior to most recent screening.

Baseline number of inpatient hospitalizations for severe VOCs will be calculated based on annualized number of hospitalizations for severe VOCs during the 2 years prior to most recent screening.

Baseline duration of inpatient hospitalizations for severe VOCs will be calculated during the 2 years prior to most recent screening. If a hospitalization started before 2 years prior to most recent screening but ended after 2 years prior to most recent screening, the entire duration of this hospitalization will be counted in the baseline and the total baseline time will change from 2 years to the start date of this hospitalization to most recent screening.

Baseline units of RBCs transfused for SCD-related indications will be calculated based on RBCs transfused for SCD-related indications during the 2 years prior to most recent screening.

For hemolysis markers, reticulocytes, total bilirubin, and indirect bilirubin, if there are multiple measurements before mobilization, use the most recent one prior to start of exchange transfusions. If it's missing, then use the one most distant from last exchange transfusion prior to this measurement and still before start of mobilization.

Change (absolute change) from baseline will be calculated as Post-baseline value - Baseline value.

Relative change from baseline will be calculated and expressed in percentage as 100%× (Post-baseline value - Baseline value) / Baseline value.

Relative reduction from baseline will be calculated and expressed in percentage as 100%× (Baseline value – Post-baseline value) / Baseline value.

Unscheduled Visits: In general, measurements obtained at unscheduled visits will be included in the analyses according to the visit windowing rules.

Visit Windowing Rules: Appendix B defines the windows for protocol visits. The windows will be applied using the following rules for both scheduled and unscheduled visits:

- If no measurement is available within a visit window, the assessment will be considered missing for the visit.

- If there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there is no record at the scheduled visit, then
    a. The record closest to the target day will be used, or
    b. If there are multiple records with the same distance to the target day, the latest record will be used.
- Assessments at early termination of follow-up (ETF) visit will follow the windowing rules for regular visits in each stage.

Incomplete/Missing data will not be imputed, unless otherwise specified. For subjects who are lost to follow-up or die, safety and efficacy analyses will be based on their available data before death or loss to follow-up. Month is defined as 30 days.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless otherwise specified.

Additional considerations for the statistical analyses are listed as follows:

- An individual subject data listing will be provided for subjects' visits impacted by COVID-19.
- Subjects with Gilbert's syndrome will be excluded from the summary of indirect bilirubin in baseline characteristics and the secondary efficacy analysis of indirect bilirubin.
- The hemoglobin assessments from central laboratories will be used for the baseline characteristics and efficacy analyses. The hemoglobin assessments from local and central laboratories will be used for the safety analyses.
- For subjects who have received the prohibited medications for SCD (HU, L-Glutamine, Crizanlizumab, or Voxelotor) post CTX001 infusion, the prohibited medication treatment period will be defined as the period from the first dose of the prohibited medication to 3 months after the last dose of the prohibited medication. The prohibited medication treatment period will be excluded in the analysis of the primary and key secondary efficacy endpoints. After CTX001 infusion, the VOC free period occurring before and after the prohibited medication treatment period will be considered consecutive unless an adjudicated severe VOC occurs during the prohibited medication treatment period.

9.2 Subject Disposition and Baseline Characteristics

9.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized as appropriate based on the Enrolled Set:

- Subjects who have been enrolled
- Subjects who have been mobilized (i.e., Safety Analysis Set)
- Subjects who underwent conditioning

- Subjects who have been dosed with CTX001 (i.e., Full Analysis Set)
- Subjects who have completed study (with 24 months post-CTX001 infusion)
- Prematurely discontinued the study with reasons for discontinuation
- Prematurely discontinued the study but enrolled into the long-term follow-up study, if any

A listing will be provided for subjects who discontinued from the study, along with reasons for discontinuation.

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS. Selected demographic data may be summarized based on the Early Efficacy Set. Baseline characteristics will also be summarized based on PES, and by subgroups of age at screening, genotype, and sex based on FAS. A listing of demographics, medical history and baseline characteristics will be provided based on the Enrolled Set.

Demographic data will include the following:

- Age at screening (in years)
- Age category at screening (<18, and ≥18 years)
- Sex (female and male)
- Ethnicity
- Race

The following baseline and disease characteristics will be summarized:

- Weight (kg)
- Height (cm)
- Genotype
- Baseline HbF level (in absolute value and %)
- Baseline total hemoglobin level
- Baseline indirect bilirubin, haptoglobin, LDH
- Number and annualized rate of severe VOCs during the 2 years prior to most recent screening
- Number and annualized rate of inpatient hospitalizations for severe VOCs during the 2 years prior to most recent screening
- Duration and annualized duration of inpatient hospitalizations for severe VOCs during the 2 years prior to most recent screening
- Total and annualized units of RBCs transfused for SCD-related indication during the 2 years prior to most recent screening

9.2.3 Medical history

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by system organ class and preferred term.

9.2.4 Prior and Concomitant Medications

Medications used in this study will be coded by the World Health Organization Drug Dictionary (WHODD) and categorized as the following:

- **Prior medication:** any medication that started before CTX001 infusion
- **Concomitant medication:** medication continued or newly received on or after CTX001 infusion until 24 months of post-infusion.

A given medication may be classified as a prior, a concomitant, or both prior and concomitant. If a medication has a completely missing or partially missing start/end date and it cannot be determined whether it was taken before the CTX001 infusion, it will be classified as prior and concomitant.

Prior and concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) levels and preferred name. The summaries will be presented by each period, based on the subset of Safety Analysis Set followed beyond the start date of a specific period. Listings by subject will also be provided. Listing of subjects receiving Thrombopoietin (TPO) after CTX001 infusion will be provided.

The logic to decide the category of a medication is presented in Appendix C.

9.2.5 Study Drug Exposure

Summary of mobilization will be provided based on FAS overall and by subgroups of age at screening and sex. Summary of conditioning will be provided based on FAS overall and by subgroups of age at screening and sex.

Summary of proportion of alleles with intended genetic modification in CTX001 drug product will be provided based on PES and FAS. Summary of CTX001 dosing will be provided based on PES overall and based on FAS overall and by subgroups of age at screening, genotype, and sex.

Summary of post-CTX001 infusion follow-up duration will be provided overall and by subgroups of age at screening, genotype, and sex.

Listing of all patients receiving mobilization agents, busulfan conditioning, AUC of busulfan concentration, and CTX001 infusion will be provided.

9.2.6 Study Drug Compliance

Not applicable.

9.2.7 Important Protocol Deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that

may significantly affect a subject's rights, safety, or well-being. IPDs will be summarized descriptively based on the FAS. All IPDs will be listed by subject.

9.3 Efficacy Analysis

9.3.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who have not experienced any severe VOC for at least 12 consecutive months (VF12) after CTX001 infusion. The evaluation of the response status of the primary efficacy endpoint for a subject starts 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management.

All severe VOCs will be adjudicated by an endpoint adjudication committee (EAC) to determine whether they meet the protocol criteria for severe VOCs. Only severe VOCs adjudicated as meeting the protocol definition of severe VOC will be counted in the primary efficacy endpoint analysis.

At the interim analyses, the analysis of VF12 will be based on the PES. The proportion of subjects who meet the primary efficacy endpoint will be provided, with the one-sided *P* value (against a 50% response rate) and the two-sided 95% exact Clopper-Pearson CI. If the prespecified efficacy boundary is crossed at any IA, overwhelming efficacy is considered established for CTX001. As a supportive analysis, the proportion of subjects who remain VOC free after 24 months post CTX001 infusion (or at the time of data cut) will be provided. In addition, VF12 will be summarized based on subjects who have been followed for at least 18 months post CTX001 infusion.

In the final analysis, the analysis of VF12 will be based on the FAS. Response evaluation period will be 24 months post CTX001 infusion for all subjects, unless a subject has died or discontinued the study. The proportion of subjects achieving VF12 will be provided with one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson CI.

A subject will be a responder if he/she meets the response criteria any time during the response evaluation period. If a subject has died or discontinued the study before achieving VF12 starting at least 60 days after the last RBC transfusion for post-transplant support or SCD management due to reasons other than CTX001-related adverse events, then the VOC free status of the subject will be carried forward up to 24 months post CTX001 infusion.

Subjects who die or discontinue the study due to CTX001-related adverse events before achieving VF12, or continuously receive RBC transfusion for post-transplant support or SCD management post CTX001 infusion after Month 10 will be considered non-responders for VF12.

All severe VOC events will be listed based on FAS, from 2 years prior to most recent screening to up to 24 months post CTX001 infusion at interim and final analyses.

Subgroup analyses of the primary efficacy endpoint will be performed with point estimate and 95% confidence interval for each of the following subgroups, during interim and final

analyses. Other subgroup analyses may be performed as appropriate. Descriptive summary will be considered if a subgroup has a sample size < 5.

- Age at screening (<18, and ≥18 years)
- Genotype
- ≥3 VOCs/year for the prior 2 years at baseline

9.3.2 Analysis of Key Secondary Efficacy Endpoints

9.3.2.1 HF12

The first key secondary efficacy endpoint is the proportion of subjects free from inpatient hospitalization for severe VOCs sustained for at least 12 months (HF12) after CTX001 infusion. The evaluation of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The algorithm to identify inpatient hospitalization for severe VOCs is in Appendix H.

At interim analysis, the analysis of HF12 will be analyzed based on the PES. The proportion of subjects who meet the key secondary efficacy endpoint will be provided, with the one-sided *P* value (against a 50% response rate) and the two-sided 95% exact Clopper-Pearson CI.

In the final analysis, the analysis of HF12 will be based on the FAS. Response evaluation period will be 24 months post CTX001 infusion for all subjects, unless a subject has died or discontinued the study. The proportion of subjects achieving HF12 will be provided with one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson CI.

A subject will be a responder if he/she meets the response criteria any time during the response evaluation period. If a subject has died or discontinued the study before achieving HF12 starting at least 60 days after the last RBC transfusion for post-transplant support or SCD management due to reasons other than CTX001-related adverse events, then the hospitalization free status of the subject will be carried forward.

Subjects who die or discontinue the study due to CTX001-related adverse events before achieving HF12, or continuously receive RBC transfusion for post-transplant support or SCD management post CTX001 infusion after Month 10 will be considered non-responders for HF12.

All inpatient hospitalization for severe VOCs will be listed, from 2 years prior to most recent screenings to up to 24 months after CTX001 infusion.

Subgroup analyses of the key secondary efficacy endpoint will be performed with point estimate and 95% confidence interval for each of the following subgroups, during interim and final analyses. Other subgroup analyses may be performed as appropriate. Descriptive summary will be considered if a subgroup has a sample size < 5.

- Age at screening (<18, and ≥18 years)

- Genotype
- ≥3 VOCs/year for the prior 2 years at baseline

9.3.2.2 VF9

The second key secondary efficacy endpoint is the proportion of subjects who have not experienced any severe VOC for at least 9 consecutive months (VF9) any time after CTX001 infusion. The evaluation of VF9 starts 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management.

A subject will be a responder if he/she meets the response criteria any time during the response evaluation period. If a subject has died or discontinued the study before achieving VF9 starting at least 60 days after the last RBC transfusion for post-transplant support or SCD management due to reasons other than CTX001-related adverse events, then the VOC free status of the subject will be carried forward up to 24 months post CTX001 infusion.

Subjects who die or discontinue the study due to CTX001-related adverse events before achieving VF9, or continuously receive RBC transfusions for more than 13 months post CTX001 infusion will be considered as non-responders for VF9.

All severe VOCs will be adjudicated by an endpoint adjudication committee (EAC) to determine whether they meet the protocol criteria for severe VOCs. Only severe VOCs adjudicated as meeting the protocol definition of severe VOC will be counted in VF9 analysis.

At the specified interim analysis, the analysis of VF9 will be based on the Early Efficacy Set. The proportion of subjects who meet VF9 will be provided, with the one-sided *P* value (against a 50% response rate) and the two-sided 95% exact Clopper-Pearson CI.

Subgroup analyses of VF9 will be performed with point estimate and 95% confidence interval for each of the following subgroups at the specified interim analysis. Other subgroup analyses may be performed as appropriate. Descriptive summary will be considered if a subgroup has a sample size < 5.

- Age at screening (<18, and ≥18 years)
- Genotype
- ≥3 VOCs/year for the prior 2 years at baseline

9.3.2.2.1 Analysis to Demonstrate VF9 as a Predictor of VF12

To demonstrate that VF9 can reasonably likely predict VF12, the number and proportion of subjects who have achieved VF12 among those who have achieved VF9 in PES will be provided. Two-sided 95% exact Clopper-Pearson CI will be provided.

Additional analyses to support VF9 as a predictor of VF12 will based on other data sources (National Heart, Lung and Blood Institute's Cooperative Study of Sickle Cell Disease, Medicaid Data and CIBMTR data).

9.3.3 Analysis of Secondary Efficacy Endpoints

At the interim analyses the analysis of secondary endpoints will be based on PES and FAS. In the final analysis, the analysis of secondary efficacy endpoints will be based on FAS. In addition, for all subjects in FAS, including those not in the PES at an IA, listings will be provided for severe VOCs and their time since CTX001 infusion, and all the secondary efficacy endpoints in the following. For subjects in FAS who are not in PES at an IA, summaries for total hemoglobin concentration, fetal hemoglobin concentration, proportion of alleles with intended genetic modification present in peripheral blood leukocytes, proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow, and PROs will be provided.

- Descriptive summary will be provided for subjects who have not achieved VF12 but have achieved at least 90%, 80%, 75%, 50% reduction from baseline in annualized rate of severe VOCs up to 24 months starting after Month 12 post CTX001 infusion. For baseline and post baseline, only adjudicated severe VOC events will be included.
- Descriptive summary will be provided for relative reduction from baseline in annualized rate of severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved VF12. For baseline and post baseline, only adjudicated severe VOC events will be included. Severe VOCs after CTX001 infusion will also be plotted.
- Duration of severe VOC free in subjects who have achieved VF12 will be summarized as mean, standard deviation (SD), median, minimum value (min), and maximum value (max). The evaluation starts 60 days after last RBC transfusion for post-transplant support or SCD management.
- Descriptive summary will be provided for relative reduction from baseline in annualized rate of inpatient hospitalizations for severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved HF12. Inpatient hospitalizations for severe VOCs after CTX001 infusion will also be plotted.
- Descriptive summary will be provided for relative reduction from baseline in annualized duration of inpatient hospitalizations for severe VOCs up to 24 months starting after Month 12 post CTX001 infusion for subjects who have not achieved HF12.
- Proportion of subjects with sustained HbF ≥20% at the time of analysis for at least 3 months, 6 months, or 12 months, starting 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. These proportions will be calculated with the corresponding two-sided 95% exact Clopper-Pearson CI.
- Descriptive summary will be provided for relative reduction from baseline in number of units of red blood cells (RBC) transfused for SCD-related indications up to 24

months starting after Month 12 post CTX001 infusion. Details of imputing missing transfusion date are described in Appendix E.

- HbF (in absolute value and %) will be summarized as a continuous variable over time.
- Hb concentrations will be summarized as a continuous variable over time.
- Change from baseline in reticulocyte count (percent reticulocytes and absolute reticulocyte count) will be summarized as a continuous variable over time.
- Change from baseline in indirect bilirubin will be summarized as a continuous variable over time.
- Change from baseline in haptoglobin will be summarized as a continuous variable over time.
- Change from baseline in lactate dehydrogenase will be summarized as a continuous variable over time.
- Proportion of alleles with intended genetic modification present in peripheral blood leukocytes will be summarized as a continuous variable over time.
- Proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow will be summarized as a continuous variable over time.
- Change from baseline in PROs (NRS, FACT-BMT, ASCQ-Me, EQ-5D-5L for subjects ≥ 18 years; NRS, PedsQL, PedsQL SCD module, EQ-5D-Y) will be summarized as a continuous variable over time including dimensional score and total score (if applicable). The derivation of the score will based on each PRO scoring manual in Appendix I.

Total hemoglobin concentration, fetal hemoglobin concentration, proportion of alleles with intended genetic modification present in peripheral blood leukocytes, proportion of alleles with intended genetic modification present in CD34+ cells of the bone marrow will also be summarized for the subgroups of age at screening, genotype, and sex based on FAS.

9.3.4 Adjustment for Multiple Comparisons

The multiplicity issues arise from testing the null hypothesis for the primary and key secondary efficacy endpoints across three interim analyses and the final analysis. The familywise type I error rate will be controlled by an alpha spending approach for tests at interim and final analyses and a sequential testing of the primary and key secondary efficacy endpoints (i.e., the key secondary efficacy endpoint will be tested only if the primary efficacy endpoint has crossed an efficacy boundary).

The following efficacy boundaries for the primary (VF12) and the first key secondary efficacy endpoints (HF12) are specified to control the type I error at one-sided 2.5% across multiple looks, based on the exact binomial distribution (Table 9-1). The key secondary endpoint VF9 based on the Early Efficacy Set will be tested only one time, with approximately 30 subjects in the early efficacy set, which is expected to occur at the time of IA2. If both VF12 and HF12 based on PES cross their efficacy boundaries, the key secondary

endpoint VF9 based on the Early Efficacy Set will be tested with a targeted one-sided alpha of 2.5%.

Table 9-1 Efficacy Boundaries and Probability of Crossing Efficacy Boundary under Null Hypothesis for Primary and Key Secondary Efficacy Endpoints based on PES at the Interim and Final Analyses

Analysis Time Point	Efficacy Boundary	Alpha spent at each IA or Final assuming a Response Rate of 50%)
IA 1: N=10	9/10	1.074%
IA 2: N=17	14/17	0.366%
IA 3: N=30	22/30	0.540%
Final: N=45	31/45	0.440%
Overall α Spending		2.420%

9.4 Safety Analysis

The overall safety profile of study will be assessed in terms of the following safety and tolerability endpoints:

- Engraftment
- AEs, SAEs, laboratory values, and vital signs from signing of informed consent through the Month 24 visit
- Mortality, including all-cause mortality and transplant-related-mortality

Safety analysis will be based on Safety Analysis Set, unless specified otherwise. All safety endpoints will be listed by subject.

9.4.1 Engraftment

Neutrophil engraftment is defined as the first day of 3 consecutive measurements of absolute neutrophil count (ANC) ≥500/μL on three different days, achieved within 42 days post CTX001 infusion (Study Day 43), without use of the unmodified $CD34^+$ cells after reaching the nadir, defined as ANC<500/μL. Neutrophil engraftment will be summarized based on the subset of the Safety Analysis Set who received CTX001 with at least 42 days follow-up post CTX001 infusion. The number and proportion (with the two-sided 95% exact Clopper-Pearson CI) of subjects achieving neutrophil engraftment, and the same summaries for achieving neutrophil engraftment within 42 days post CTX001 infusion will be provided. Time from CTX001 infusion to neutrophil engraftment will be summarized as a continuous variable (with mean, SD, median, min and max) and plotted with a Kaplan-Meier curve for subjects who have achieved neutrophil engraftment.

Platelet engraftment is defined as the first day of three consecutive measurements of unsupported (no platelet transfusions for the last 7 days) platelet ≥50,000/μL on 3 different days after CTX001 infusion after reaching nadir, defined as platelet <50,000/μL, or the first platelet transfusion whichever is earlier. For subjects who were discharged before reaching platelet engraftment, platelet engraftment will be defined as the 7^{th} day after the last platelet transfusion, if there were 3 subsequent and consecutive unsupported measurements of

unsupported platelet ≥50,000/μL on 3 different days. This last platelet transfusion refers to the last platelet transfusion preceding these 3 measurements. Time from CTX001 infusion to platelet engraftment will be summarized as a continuous variable (with mean, SD, median, min and max) and plotted with a Kaplan-Meier curve for subjects who have achieved platelet engraftment.

9.4.2 Adverse Events

For analysis purposes, AEs and SAEs will be summarized for the period from Enrollment to End of Study Visit (or until data cut at an IA), the period from CTX001 infusion to End of Study Visit (or until data cut at an IA), and for the additional analysis periods (until data cut at an IA) as outlined in Table 9-2.

Table 9-2 Additional analysis periods for AE and SAE Summary

Study Time Period
Enrollment to the day before the first mobilization cycle
Start of first mobilization cycle to the day before the start of busulfan conditioning
Start of busulfan conditioning to neutrophil engraftment
The day after neutrophil engraftment to Month 24 Visit (End of Study Visit)
Enrollment to the day before CTX001 infusion

If back-up cells are needed, engraftment date will be determined by the engraftment date to the back-up cells.

For AEs/SAEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs/SAEs started before or after certain period, the AEs/SAEs will be classified to be in this period. Details for imputing missing or partial missing start dates of adverse events are described in Appendix D.

The number and percentage of subjects with adverse events will be summarized by severity, seriousness, relationship to the study drug, MedDRA system organ class, and preferred term according to the time periods and post-CTX001 infusion onset time intervals (e.g., every 3 or 6 months after CTX001 infusion). The number and percentage of subjects with AEs and SAEs within each period will be based on the subset of the Safety Analysis Set being followed beyond the start of that period. Subjects with multiple occurrences of the same AE/SAE within the same study period will be counted once. AEs of the maximum severity level will be presented in summaries by AE severity; AEs of the strongest relationship will be presented in summaries by AE relationship; AEs of the maximum seriousness will be presented in the summaries of SAEs. AE subgroup analyses will also be provided for the subgroups of age at screening, genotype, race, region, and sex. In addition, a listing containing individual subject adverse event data for SAEs and deaths will be provided separately. All AEs/SAEs will be presented in an individual subject data listing.

9.4.3 Occurrence of TRM

The transplant-related mortality is defined as death related to Busulfan and/or CTX001 infusion. The number and proportion (with the two-sided 95% exact Clopper-Pearson CI) of TRM within 100 days will be summarized for subjects who have died within 100 days, or with at least 100 days post CTX001 infusion. The number and proportion (with the two-sided

95% exact Clopper-Pearson CI) of TRM within 12 months will be summarized for subjects who have died within 12 months, or with at least 12 months post CTX001 infusion. All TRM will be listed by subject.

9.4.4 All-cause Mortality

All-cause mortality after screening till the end of the study will be listed.

9.4.5 Clinical Laboratory

For laboratory measurements, the raw values and change from baseline values of the hematology, chemistry, coagulation, and immunology results will be summarized in SI units by visit. For selected laboratory measurements, the number and percentage of subjects meeting potentially clinically significant thresholds will be summarized. The shift from baseline will also be summarized for selected parameters. The criteria for threshold analysis are in Appendix J. In addition, hematology, chemistry, coagulation, and immunology results will be listed by subject. This listing will include data from both scheduled and unscheduled visits. The visit schedule is in Appendix A.

9.4.6 Electrocardiogram

A summary of raw values and change from baseline values will be provided by visit for the following standard 12-lead ECG measurements: RR (msec), HR (bpm), PR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]). The number and percentage of subjects meeting potentially clinically significant thresholds will be summarized. The criteria for threshold analysis are in Appendix J. A listing of all ECG measurements, including measurements from scheduled and unscheduled visits, will be provided based on the Safety Analysis Set. The visit schedule is in Appendix A.

9.4.7 Vital Signs

For vital signs measurements, the raw values and change from baseline values will be summarized by visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), and pulse oximetry (%). The number and percentage of subjects meeting potentially clinically significant thresholds will be summarized. The criteria for threshold analysis are in Appendix J. A listing of all vital signs measurements, including measurements from scheduled and unscheduled visits, will be provided based on the Safety Analysis Set. The visit schedule is in Appendix A.

9.4.8 Physical Examination

PE findings will be listed by subject. The visit schedule is in Appendix A.

9.5 Exploratory Analysis

Unless specified otherwise, the analysis of the exploratory endpoints will be provided in an exploratory analysis plan.

Hemoglobin fractions and change from baseline in proportion of circulating erythrocytes expressing fetal hemoglobin (F-cells) will be summarized for subjects in FAS, PES and subjects in FAS who are not in PES at an IA. They will also be summarized for the subgroups of age at screening, genotype, and sex based on FAS.

10 SUMMARY OF INTERIM AND DMC ANALYSES

10.1 Interim Analysis

With a total of 45 dosed subjects, 3 IAs may be performed following a group sequential testing procedure in the expanded study to allow for early evaluation of efficacy. The first/second/third IA will be conducted when the primary efficacy set consists of approximately 10/17/30 subjects. The actual alpha spending will be based on the number of subjects in the primary efficacy set at the IA. If an IA is not conducted, alpha planned for this IA will be recovered in the subsequent analysis. Vertex Biometrics will conduct the statistical analyses for the interim and the final reports.

For interim analyses, the number of subjects in analysis sets will be tabulated. Subject disposition will be summarized based on the Enroll Set, and demographics and baseline characteristics specified in Section 9.2 will be summarized based on FAS. Efficacy analysis will be provided as specified in Section 9.3. Safety analysis will be provided as specified in Section 9.4.

10.2 DMC Analysis

An independent data monitoring committee (DMC) was formed before study initiation. The DMC's objectives, analysis plan, and operational details were defined DMC Charter and DMC SAP.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study CTX001-121: Screening (Stage 1)

Event/Assessment	Screening (Up to 8 Weeks)	Comments
Informed consent and where applicable, assent	X	Perform vital signs after consent even if collected prior to consent as part of standard of care
PRO assessment (≥18 years old): Pain scale (11-point NRS), ASCQ-Me, FACT-BMT, and EQ-5D-5L PRO assessment (<18 years old): Pain scale (11-point NRS), EQ-5D-Y, PedsQL, and PedsQL SCD module	X	Perform as the first assessment after signing informed consent (Protocol Section 11.12).
Demographics	X	Protocol Section 11.1
Medical history	X	Including medical records on SCD-related complications and associated treatment including medical facility visits, inpatient hospitalizations and transfusion records for at least 2 years before consent will be collected
Full physical examination[b]	X	Including assessment of spleen size, skin ulcers, and signs/symptoms consistent with myocardial infarction or cerebral vascular accident, new or worsening osteonecrosis, and retinopathy (Protocol Section 11.15.3)
Performance status	X	Protocol Section 11.15.3
Height and weight	X	Measure with shoes off
Vital signs	X	Includes blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry (Protocol Section 11.15.3)
SCD genotyping (central laboratory)	X	All subjects will be genotyped for SCD (alpha and *HBB* loci) to confirm βS/βS, βS/β0 or βS/β^+ genotype. Results will be required before busulfan conditioning begins.
Serum chemistry	X	Protocol Section 11.15.2
Coagulation	X	Protocol Section 11.15.2
Hematology	X	Protocol Section 11.15.2
Serum pregnancy test	X	For females of childbearing potential (Protocol Section 11.15.6)
Hemoglobin fractionation (central laboratory)	X	HbF for establishing eligibility; will also include HbS, HbA2, HbA.

Table 11-1 Study CTX001-121: Screening (Stage 1)

Event/Assessment	Screening (Up to 8 Weeks)	Comments
Infectious disease marker testing	X	Infectious disease marker testing will include HBV (HBcAb, HbsAg, and NAT); HCV (HCAb and NAT); HIV-1, HIV-2 (Antigen/Antibody immunoassay, if positive, then NAT); and syphilis[a] HTLV-1 Ab (if applicable) (Protocol Section 11.15.2)
Urinalysis	X	Protocol Section 11.15.2
12-lead ECG	X	Protocol Section 11.15.5
Brain MRI/MRA	X	To confirm absence of active Moyamoya disease. If a brain MRI/MRA was performed within 3 months before date of consent, these results may be used, unless repetition of the assessment is clinically indicated (Protocol Section 11.4)
Transcranial Doppler (TCD) ultrasound	X	For subjects 12 to 16 years of age (Protocol Section 11.4)
Echocardiograph	X	LVEF, TRV, and E/e' assessment (Protocol Section 11.4)
DLco [corrected]	X	Protocol Section 11.3
Adverse event assessment	X	Continuous from ICF signing and assent (where applicable)
Prior and concomitant medications	X	Continuous from ICF signing and assent (where applicable)

[a] Subjects must have at least a screening assay for syphilis performed (e.g., rapid plasma reagin [RPR] is preferred). If positive, a confirmatory test (e.g., FTA-ABS, TPPA) must be done to confirm the presence of active infection. Local testing algorithms for syphilis may be used, provided they contain these tests.
[b] Including Tanner Staging for subjects 12 to <18 years old who have not reached Tanner Stage 5.

Table 11-2 Study CTX001-121: Pre-mobilization Period and Autologous CD34+ Stem Cell Apheresis (Stage 1 and Stage 2)

			Mobilization and Apheresis[b]			
Event/Assessment	**After Eligibility Confirmation (Before Mobilization Start)** [a,b]	**Day -5 to Day -1**[a]	**Day 1**	**Day 2**	**Day 3 (if needed)**	**Comments**
Blood allelic editing (central laboratory)[c]	X					Peripheral blood sample; Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.7)
Immunological testing[c]	X					Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.15.2)
HbF distribution, F-cells (central laboratory)[c]	X					Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.7)
Inflammatory and endothelial activation markers (central laboratory)[c]	X					Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.7)
N-terminal prohormone b-type natriuretic peptide[c] (NT-proBNP; central laboratory)	X					Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.7)
Bone marrow aspirate (central laboratory)	X					Collect before start of first cycle only. Baseline sample for genomic analysis, and exploratory biomarkers (Protocol Section 11.9).
Exploratory biomarker samples (central laboratory)[c]	X					Collect before start of first RBC exchange or simple transfusion (Protocol Section 11.7.1)
Urine sample collection (central laboratory)	X					For urine albumin to creatinine ratio Collect first morning void (Protocol Section 11.5)
Sperm or oocyte banking	X (optional)					If requested by subject or their legally authorized representative, if less than 18 years of age, prior to busulfan conditioning. Gonadal tissue banking may be done as appropriate per subject age and local site practice. (Protocol Section 11.10)
Infectious disease marker testing	X					Repeated within 28 days before the start of each planned apheresis cycle and results should be reported at least 5 business days before each planned cycle (Protocol Section 11.15.2)
Mini-Mental State Examination (subjects ≥18 years old) or Wechsler Abbreviated Scale of Intelligence (subjects <18 years old)	X					Age at time of assessment For subjects already on a transfusion regimen MMSE and WASI should be administered before the first mobilization/apheresis cycle. Protocol Section 11.13 (MMSE), Protocol Section 11.14 (WASI)
Hemolysis markers[c]	X					Collect before start of first RBC exchange or simple transfusion. Hemolysis markers include haptoglobin and lactate dehydrogenase (Protocol Section 11.15.2)
Erythropoietin[c] (central laboratory)	X					Collect before start of first RBC exchange or simple transfusion. Protocol Section 11.15.2.

Table 11-2 Study CTX001-121: Pre-mobilization Period and Autologous CD34+ Stem Cell Apheresis (Stage 1 and Stage 2)

			Mobilization and Apheresis[b]			
Event/Assessment	**After Eligibility Confirmation (Before Mobilization Start)** [a,b]	**Day -5 to Day -1**[a]	**Day 1**	**Day 2**	**Day 3 (if needed)**	**Comments**
Methemoglobin[c]	X					Collect before start of first RBC exchange or simple transfusion. Protocol Section 11.15.2.
Ferritin[c]	X					Collect before start of first RBC exchange or simple transfusion. Protocol Section 11.15.2.
Serum pregnancy test		X				Females of childbearing potential only. Must be performed within 3 days prior to starting **each** mobilization.
Eligibility for mobilization/apheresis re-confirmed		X				Per site's standard guidelines. Subject must be hemodynamically stable and have no active infection per investigator judgment.
Abbreviated physical examination		X	X	X	X	Prior to each cycle and daily before mobilization (plerixafor) or before the start of apheresis (Protocol Section 11.15.3)
Performance status		X	X	X	X	Prior to each cycle and daily before mobilization (plerixafor) or before the start of apheresis (Protocol Section 11.15.3)
Vital signs		X	X	X	X	Prior to each cycle and daily before mobilization (plerixafor) or before the start of apheresis. Includes blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry (Protocol Section 11.15.3)
Weight		X				Measure with shoes off
12-lead ECG			X			Before mobilization (plerixafor) or before the start of apheresis on Day 1 of each cycle (Protocol Section 11.15.5)
Hematology		X	X	X	X	Prior to each cycle and immediately before starting apheresis on Days 1 through Day 3. (Protocol Section 11.15.2)
Serum chemistry		X	X	X	X	Prior to each cycle and daily before mobilization (plerixafor) or before the start of apheresis. (Protocol Section 11.15.2)
Coagulation		X	X	X	X	Prior to each cycle and daily before mobilization (plerixafor) or before the start of apheresis. (Protocol Section 11.15.2)
Placement of central venous catheter for apheresis	X (if needed)					
Pre-mobilization RBC exchange transfusion regimen	X					Refer to Table 11-5
Plerixafor administration			X	X	X	Plerixafor will be administered 2 to 3 hours before the start of each day of apheresis. Plerixafor will be administered only if apheresis collection is planned for that day. Administration time can be adjusted based on $CD34^+$ kinetics and in conversation with the study medical monitor and the apheresis specialist.

Table 11-2 Study CTX001-121: Pre-mobilization Period and Autologous CD34+ Stem Cell Apheresis (Stage 1 and Stage 2)

			Mobilization and Apheresis[b]			
Event/Assessment	**After Eligibility Confirmation (Before Mobilization Start)** [a,b]	**Day -5 to Day -1**[a]	**Day 1**	**Day 2**	**Day 3 (if needed)**	**Comments**
$CD34^+$ count			X	X	X	$CD34^+$ cells must be counted before plerixafor administration, 2 hours (± 15) minutes, 4 hours (± 15) minutes, and 6 hours (± 15) minutes post plerixafor administration. $CD34^+$ cells must be counted within 30 minutes after completion of apheresis. Sites may perform additional peripheral $CD34^+$ counts per local standards
Apheresis and shipment of $CD34^+$ stem cells to central manufacturer			X	X		Target to process 22 liters (approximately 4 total blood volumes). For the mobilization/apheresis cycle, cells should be shipped to central manufacturer at the end of Day 1 and Day 2. After the first cycle, cells may be collected for manufacturing on Day 1 and Day 2 (as needed)
Apheresis for $CD34^+$ backup stem cells[d]					X	For the first mobilization/apheresis cycle, $CD34^+$ cells will be collected for backup on Day 3 only. After the first cycle, $CD34^+$ cells may be collected for backup on any day after sufficient $CD34^+$ cells are collected for manufacturing. Cells collected for backup will be stored at the study site. Backup $CD34^+$ cells may also be collected on manufacturing cell collection days ONLY after enough cells have been collected for manufacturing and after discussion with the medical monitor and apheresis specialist.
HbS and Hb levels			X	X[e]	X[e]	Daily before mobilization (plerixafor) or before the start of apheresis (Protocol Section 11.2)
Adverse event assessment	Continuous from signing ICF and assent (where applicable)					
Prior and concomitant medications	Continuous from signing ICF and assent (where applicable)					

[a] Assessments may be performed over multiple days or visits

[b] In addition to study-related visits, additional assessments or visits may be performed per institutional guidelines or as deemed appropriate by the investigator.

[c] For subjects on chronic transfusion, should be collected within 1 week of a subsequent RBC exchange or simple transfusion and before the first mobilization/apheresis cycle.

[d] For subsequent cycles (after the first mobilization/apheresis cycle) Days 2 and 3 of apheresis will be performed as needed.

[e] HbS collected on Day 2 or Day 3 only if a VOC or other serious adverse event has occurred.

Table 11-3 Study CTX001-121: Myeloablative Conditioning and Infusion of CTX001 (Stages 3A/3B)

Event/Assessment	Pre-conditioning[a,b]		Conditioning[b]	Infusion[b]	Comments
	30 to 7 Days Before Busulfan Initiation	3 to 7 Days Before Busulfan Initiation	Day -5 to -2	Day 1	
Serum pregnancy test		X			Females of childbearing potential only. Must be performed within 5 days of starting busulfan
Abbreviated physical examination		X	X	X	Protocol Section 11.15.3
Performance status		X	X	X	Protocol Section 11.15.3
Vital signs		X	X	X	Includes blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry. Day 1: before starting infusion of the first vial of CTX001, at 30 (±5) minutes after start of CTX001 infusion, then every 30 (± 5) minutes through 2 hours after the last vial of CTX001 has infused (Protocol Section 11.15.3)
Weight		X			Measured with shoes off
12-lead ECG		X		X	Day 1: ECGs before start of infusion (Protocol Section 11.15.5
Hematology		X	X	X	Day 1: Collect laboratory assessments before start of infusion (Protocol Section 11.15.2)
Serum chemistry		X	X	X	Day 1: Collect laboratory assessments before start of infusion (Protocol Section 11.15.2)
Eligibility for myeloablation reconfirmed	X	X			30 to 7 days before busulfan initiation: If screening examination and start of pre-conditioning visit (30 days prior to busulfan) are ≥4 months apart, repeat pulmonary function tests and echocardiograph 3 to 7 days before busulfan initiation: Review most recent assessments (within 7 days prior to conditioning) as per site's standard guidelines for autologous stem cell transplant.
Pre-conditioning transfusion regimen	X				Refer to Table 11-5. Treatment with HU, crizanlizumab (ADAKVEO®), and voxelotor (OXBRYTA®) should be stopped at least 8 weeks before planned mobilization.
Confirm rescue cells are cryopreserved in acceptable condition at the site		X			
Confirm central line is placed		X			
Confirm CTX001 was received in acceptable condition at the site prior to initiating busulfan			X		
Test dose of busulfan to determine optimal busulfan dose[c]	X (optional)				
Anti-seizure prophylaxis[e]			X		Initiate anti-seizure prophylaxis at least 12 hours before first dose of busulfan per hospital guidelines
IV busulfan administration[c]			X		Protocol Section 9.8.3

Table 11-3 Study CTX001-121: Myeloablative Conditioning and Infusion of CTX001 (Stages 3A/3B)

Event/Assessment	Pre-conditioning[a,b]		Conditioning[b]	Infusion[b]	Comments
	30 to 7 Days Before Busulfan Initiation	3 to 7 Days Before Busulfan Initiation	Day -5 to -2	Day 1	
Busulfan PK	X[d]		X		Blood sample will be collected for PK analysis for busulfan on Day 1 and Day 3 of conditioning as per Protocol Appendix 15.1
IV infusion of CTX001				X	Subjects should be pre-medicated with an antihistamine (diphenhydramine hydrochloride) and an antipyretic (acetaminophen or paracetamol) per institutional guidelines (Protocol Section 10.1.4)
Adverse event assessment	Continuous from signing ICF and assent (where applicable)				
Prior and concomitant medications	Continuous from signing ICF and assent (where applicable)				

[a] Assessments may be performed over multiple days of visits.

[b] In addition to study-related visits, subjects will be followed per institutional guidelines or as deemed appropriate by the investigator.

[c] For subjects less than 34 kg, weight-based recommendation for busulfan dosing are according to Trame et al., 2001 provided that the target AUC is the same (Protocol Section 9.8.3).

[d] PK analysis will be performed if the test dose of busulfan is administered.

[e] Phenytoin is contraindicated.

Table 11-4 Study CTX001-121: Post-infusion Through Follow-up (Stage 4)

Event/ Assessment	Daily From Day 2 Until Discharge	Follow-up[a,b]													Comments
		D+30[c]	D+60	D+90	D+120	D+150	D+180	D+270	D+360	D+450	D+540	D+630	D+720		
		M1 (±4d)	M2 (±7d)	M3 (±7d)	M4 (±7d)	M5 (±7d)	M6 (±14d)	M9 (±14d)	M12 (±14d)	M15 (±14d)	M18 (±14d)	M21 (±14d)	M24 (±14d)	ETF[cd]	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry. (Protocol Section 11.15.3)
Physical examination									X[e]				X[e]	X	Protocol Section 11.15.3
Abbreviated physical examination	X	X	X	X	X	X	X	X		X	X	X			Protocol Section 11.15.3
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Protocol Section 11.15.3
Post CTX001 infusion transfusion regimen							X								Refer to Table 11-5
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Platelet levels will be monitored daily in the hospital and every 2 to 3 days after discharge until platelet engraftment is achieved (Protocol Section 11.15.2)
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Protocol Section 11.15.2
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Protocol Section 11.15.2
Hemolysis markers		X		X			X	X	X	X	X	X	X	X	Hemolysis markers include haptoglobin and lactate dehydrogenase (Protocol Section 11.15.2)
Erythropoietin (central laboratory)				X			X	X	X		X		X	X	Protocol Section 11.15.2
Methemoglobin				X			X	X	X		X		X	X	Protocol Section 11.15.2
Ferritin									X				X	X	Protocol Section 11.15.2
Immunological testing				X			X		X				X	X	Protocol Section 11.15.2

Table 11-4 Study CTX001-121: Post-infusion Through Follow-up (Stage 4)

Event/ Assessment	Daily From Day 2 Until Discharge	Follow-up[a,b]												Comments
		D+30[c]	D+60	D+90	D+120	D+150	D+180	D+270	D+360	D+450	D+540	D+630	D+720	
		M1 (±4d)	M2 (±7d)	M3 (±7d)	M4 (±7d)	M5 (±7d)	M6 (±14d)	M9 (±14d)	M12 (±14d)	M15 (±14d)	M18 (±14d)	M21 (±14d)	M24 (±14d)	ETF[cd]	
Blood allelic editing (central laboratory)		X	X	X	X	X	X	X	X		X		X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7)
Hemoglobin fractionation (central laboratory)		X	X	X	X	X	X	X	X	X	X	X	X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7)
HbF distribution, F-cells (central laboratory)		X	X	X	X	X	X	X	X	X	X	X	X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7)
Inflammatory and endothelial activation markers (central laboratory)				X			X		X		X		X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7)
NT-proBNP level (central laboratory)									X		X		X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7)
Exploratory biomarker blood samples (central laboratory)				X			X		X		X		X	X	Before scheduled transfusion (if applicable) (Protocol Section 11.7.1
Bone marrow aspirate (central laboratory)							X		X				X	X	For assessment of allelic editing, and exploratory biomarkers (Protocol Section 11.9)
Urine sample collection (central labratory)									X				X	X	For urine albumin to creatine ratio Collect first morning void (Protocol Section 11.5)
DLco [corrected]									X				X	X	Protocol Section 11.3
Echocardiograph									X		X		X	X	TRV, LVEF, and E/e' assessment (Protocol Section 11.4)
12-lead ECG									X				X	X	Protocol Section 11.15.5

Table 11-4 Study CTX001-121: Post-infusion Through Follow-up (Stage 4)

Event/ Assessment	Daily From Day 2 Until Discharge	Follow-up[a,b]													Comments
		D+30[c]	D+60	D+90	D+120	D+150	D+180	D+270	D+360	D+450	D+540	D+630	D+720		
		M1 (±4d)	M2 (±7d)	M3 (±7d)	M4 (±7d)	M5 (±7d)	M6 (±14d)	M9 (±14d)	M12 (±14d)	M15 (±14d)	M18 (±14d)	M21 (±14d)	M24 (±14d)	ETF[cd]	
PRO assessments For ≥18 years of age: EQ-5D-5L, FACT-BMT, and ASCQ-Me For <18 years of age: EQ-5D-Y, PedsQL, and PedsQL SCD module				X			X		X		X		X	X	Assessment should be performed as the first assessment at any visit if possible (Protocol Section 11.12)
PRO assessments (Pain-Scale [11-point NRS])				X	X	X	X	X	X	X	X	X	X	X	Assessment should be performed as the first assessment at any visit if possible (Protocol Section 11.12)
Adverse event collection	Continuous from signing ICF and assent (where applicable)														
Prior and concomitant medication	Continuous from signing ICF and assent (where applicable)														

[a] Assessments may be performed over multiple days of visits.

[b] In addition to study-related visits, subjects will be followed per institutional guidelines or as deemed appropriate by the investigator.

[c] Month (M) is defined as 30 days. If Day 30/M1 occurs while the subject is still hospitalized, the daily assessments required before discharge should be done in addition to the Day 30/M1 assessments.

[d] Early Termination of Follow-Up (ETF). Assessments performed within 2 weeks of ETF Visit should not be repeated. Echocardiograph, DLco, and bone marrow aspirate should not be repeated if performed within 6 months of ETF Visit.

[e] Includes Tanner Staging for subjects 12 to <18 years old until they reach Tanner Stage 5.

Table 11-5 Study CTX001-121: Transfusion Regimen

Event/ Assessment	Pre-mobilization	Prior to Mobilization and Apheresis	Pre-conditioning		After Start of Busulfan to CTX001 Infusion	Post CTX001 Infusion	Notes
	Minimum 8 weeks	Within 3 days	Minimum 8 weeks	Up to 7 days			
RBC exchange transfusion[a]	X[b]	X[c]	X[d]	X[c]	None	X[e]	[a] All transfusions of RBC products should be depleted of leukocytes and matched for at least the ABO blood group, the Kell (K) blood group, and Rh antigens C, D, and E [b] Initiate RBC exchange or simple transfusion a minimum of 8 weeks before planned start of mobilization with a goal of maintaining the target HbS level of <30% of total Hb while keeping total Hb concentration ≤11 g/dL; use of simple transfusions instead of exchange transfusions should be made in consultation with the medical monitor. Treatment with HU, crizanlizumab (ADAKVEO), and voxelotor (OXBRYTA) should be stopped at least 8 weeks before planned mobilization. [c] Subjects should receive an RBC exchange or simple transfusion; use of simple transfusions instead of exchange transfusions should be made in consultation with the medical monitor. [d] Continue or reinitiate RBC exchange or simple transfusion a minimum of 8 weeks before start of busulfan conditioning with a goal of maintaining an HbS level of <30% of total Hb while keeping total Hb concentration ≤11 g/dL; use of simple transfusions instead of exchange transfusions should be made in consultation with the medical monitor. [e] As needed to maintain Hb ≥7 g/dL per institutional standards.
Platelet transfusions						X	Target to maintain platelets >50,000/μL
HbS and Hb levels	X	X	X	X			Collect prior to and after each RBC exchange or simple transfusion, including the RBC exchange or simple transfusion required within 3 days before the start of each mobilization and apheresis cycle (Protocol Section 11.2)

Appendix B: Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements after CTX001 Infusion

Table 11-6 Visit Window Mapping Rules

Assessment[a]	Visit	Target Study Day[b]	Visit Window (in study Days)
Vital signs Performance status Hematology Serum chemistry Coagulation Hemoglobin fractionation (central laboratory) HbF distribution, F-cells (central laboratory)	M1	30	[16, 45]
	M2	60	[46, 75]
	M3	90	[76, 105]
	M4	120	[106, 135]
	M5	150	[136, 165]
	M6	180	[166, 225]
	M9	270	[226, 315]
	M12	360	[316, 405]
	M15	450	[406, 495]
	M18	540	[496, 585]
	M21	630	[586, 675]
	M24	720	[676, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Abbreviated physical examination	M1	30	[16, 45]
	M2	60	[46, 75]
	M3	90	[76, 105]
	M4	120	[106, 135]
	M5	150	[136, 165]
	M6	180	[166, 225]
	M9	270	[226, 360]
	M15	450	[361, 495]
	M18	540	[496, 585]
	M21	630	[586, 675]
Hemolysis markers	M1	30	[1, 60]
	M3	90	[61, 135]
	M6	180	[136, 225]
	M9	270	[226, 315]
	M12	360	[316, 405]
	M15	450	[406, 495]
	M18	540	[496, 585]
	M21	630	[586, 675]
	M24	720	[676, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Erythropoietin (central laboratory) Methemoglobin	M3	90	[46, 135]
	M6	180	[136, 225]
	M9	270	[226, 315]

	M12	360	[316, 450]
	M18	540	[451, 630]
	M24	720	[631, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Immunological testing	M3	90	[46, 135]
	M6	180	[136, 270]
	M12	360	[271, 540]
	M24	720	[541,765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Blood allelic editing (central laboratory)	M1	30	[16, 45]
	M2	60	[46, 75]
	M3	90	[76, 105]
	M4	120	[106, 135]
	M5	150	[136, 165]
	M6	180	[166, 225]
	M9	270	[226, 315]
	M12	360	[316, 450]
	M18	540	[451, 630]
	M24	720	[631, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Inflammatory and endothelial activation markers (central laboratory) Exploratory biomarker blood samples (central laboratory) PRO assessments For ≥18 years of age: EQ-5D-5L, FACT BMT, and ASCQ-Me For <18 years of age: EQ-5D-Y, PedsQL, and PedsQL SCD module	M3	90	[46, 135]
	M6	180	[136, 270]
	M12	360	[271, 450]
	M18	540	[451, 630]
	M24	720	[631, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
Bone marrow aspirate (central laboratory)	M6	180	[91, 270]
	M12	360	[271, 540]
	M24	720	[541, 765]
	ETF[c]	N/A	Follow the individual visit window to be

			mapped to individual visits
Physical examination Ferritin DLco [corrected] Urine sample collection (central laboratory) 12-lead ECG	M12	360	[181, 540]
	M24	720	[541, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
NT-proBNP level (central laboratory) Echocardiograph	M12	360	[271, 450]
	M18	540	[451, 630]
	M24	720	[631, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits
PRO assessment (Pain-Scale [11 point NRS],)	M3	90	[46, 105]
	M4	120	[106, 135]
	M5	150	[136, 165]
	M6	180	[166, 225]
	M9	270	[226, 315]
	M12	360	[316, 405]
	M15	450	[406, 495]
	M18	540	[496, 585]
	M21	630	[586, 675]
	M24	720	[676, 765]
	ETF[c]	N/A	Follow the individual visit window to be mapped to individual visits

[a] Assessments may be performed over multiple days or visits.

[b] Month (M) is defined as 30 days. If Day 30 occurs while the subject is still hospitalized, the daily assessments required before discharge should be done in addition to the Day 30 assessments.

[c] Early Termination of Follow-Up. Assessments performed within 2 weeks of ETF Visit should not be repeated. Echocardiograph, DLco, and bone marrow aspirate should not be repeated if performed within 6 months of ETF Visit.

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only Day is missing, use the first day of the month unless it is the same month as the first mobilization start date, in that case use the first mobilization start date except in cases where this will lead to a start date being after stop date. In these situations, the original rule 'use the first day of the month' will be applied.
    b. If Day and Month are both missing, use the first day of the year unless it is the same year as the first mobilization start date, in that case use the first mobilization start date except in cases where this will lead to a start date being after stop date. In these situations, the original rule 'use the first day of the year' will be applied.
    c. If Day, Month and Year are all missing, use the first mobilization start date except in cases where this will lead to a start date being after stop date. In these situations, use 1 day prior to the stop date.
2. Missing or partial medication stop date:
    a. If only Day is missing, use the last day of the month.
    b. If Day and Month are both missing, use the last day of the year.
    c. If Day, Month and Year are all missing, assign 'continuing' status to stop date.

Table 11-7 Logic for Determining the Category of a Medication

	Medication stop date	
Medication start date	< CTX001 infusion	≥ CTX001 infusion and ≤ 24 months post-infusion
< CTX001 infusion	P	PC
≥ CTX001 infusion and ≤ 24 months post-infusion	-	C

P: Prior; C: Concomitant.

Appendix D: Imputation Rules for Missing AE Start Date

For missing or partial AE start date, use the imputation rules below.

1. Missing or partial AE start date:
    a. If only Day is missing, use the first day of the month unless it is the same month as CTX001 infusion date, in that case use CTX001 infusion date except in cases where this will lead to a start date being after stop date. In these situations, the original rule 'use the first day of the month' will be applied.
    b. If Day and Month are both missing, use the first day of the year unless it is the same year as CTX001 infusion date, in that case use CTX001 infusion date except in cases where this will lead to a start date being after stop date. In these situations, the original rule 'use the first day of the year' will be applied.
    c. If Day, Month and Year are all missing, use CTX001 infusion date except in cases where this will lead to a start date being after stop date. In these situations, use January 1, 2018 as the start day.
2. Missing or partial AE stop date:
    a. If only Day is missing, use the last day of the month.
    b. If Day and Month are both missing, use the last day of the year.
    c. If Day, Month and Year are all missing, assign 'continuing' status to stop date.

Appendix E: Imputation Rules for Missing Transfusion Date

If only Day is missing, use the first day of the month, unless there is another transfusion within 5 days; in that case use 15th of the month as the imputed date.

Appendix F: Imputation Rules for Missing Historical Unit of RBC Transfusions

1. If the volume of this transfusion is known, using this RBC transfusion volume divides the average historical RBC transfusion volume per unit as the imputed value. Using the pre-CTX001 infusion average RBC transfusion volume per unit if the average historical RBC transfusion volume per unit is not available.
2. If the volume of this transfusion is unknown: for simple transfusions: using 1 unit as the imputed value; for exchange transfusions, using the average historical exchange RBC transfusion unit for this subject as the imputed value. If the average historical exchange RBC transfusion unit is not available, using the pre-CTX001 infusion period average exchange RBC transfusion unit for this subject.

Appendix G: Imputation Rules for Missing Historical Hospitalization Duration

If the historical hospitalization duration is missing, using the average historical hospitalization duration, rounds to the nearest integer (in case .5, rounds up) for this subject as the imputed value. The missing hospitalization date will be imputed based on imputed hospitalization duration. If both start date and end date are missing, use the first day of the month as the start date if only Day is missing; use the first day of the year if Day and Month are both missing.

Appendix H: Algorithm to Identify Inpatient Hospitalizations for Severe VOCs

The following data will be inputted into the algorithm:

- All hospitalization records
- Severe VOCs which are related to inpatient hospitalization and adjudicated by EAC as meeting the protocol definition of severe VOCs

The following algorithm will be used to identify inpatient hospitalizations for severe VOCs:

- For severe VOCs with complete adjudicated start dates, the below 4 steps are implemented following the order as noted. The hospitalizations which have been identified as hospitalizations for Severe VOCs will be excluded in the subsequent step(s).
    - Step 1: If the start date of a hospitalization is within ±3 days of the adjudicated start date of a severe VOC, this hospitalization is identified as a hospitalization for this severe VOC.
    - Step 2: If a severe VOC covers the entire duration of a hospitalization, this hospitalization is identified as a hospitalization for this severe VOC.
    - Step 3: If the start date of a hospitalization is within ±7 days of the adjudicated start date of a severe VOC, this hospitalization is identified as a hospitalization for this severe VOC.
    - Step 4: If the start date of a hospitalization is within ±14 days of the adjudicated start date of a severe VOC and the end date of this hospitalization is within ±3 days of the end date of the same severe VOC, this hospitalization is identified as a hospitalization for this severe VOC.
- For severe VOCs with incomplete adjudicated start dates, a hospitalization is identified as a hospitalization for a severe VOC if the end date of this hospitalization is within ±3 days of the end date of the severe VOC.

Appendix I: Scoring Manuals for Patient Reported Outcomes

The scoring manuals for patient reported outcomes are as follows:

- EuroQol Research Foundation. EQ-5D-5L User Guide (Version 2.1, April 2015)
- ASCQ-Me User's Manual (December 2017)
- FACT-BMT Scoring Guidelines (Version 4.0)
- Scaling and scoring of the Pediatric Quality of Life Inventory (Version 17, May 2017)
- EuroQol Research Foundation. EQ-5D-Y User Guide (Version 2.0, September 2020)

Appendix J: Criteria for Threshold Analysis

Table 11-8 Threshold Analysis Criteria for Clinical Laboratory Tests

Parameter	Threshold Analysis Criteria
Hematology	
Basophils (10^9/L)	>ULN <LLN
Eosinophils (10^9/L)	>ULN <LLN
Erythrocytes (10^12/L)	>ULN <LLN
Erythrocyte distribution width (%)	>ULN <LLN
Hematocrit (ratio)	Hematocrit decreased <0.36 to >=0.30 <0.30 to >=0.24 <0.24 Hematocrit increased >0.48 to <=0.54 >0.54 to <=0.60 >0.60
Hemoglobin (g/dL)	Hemoglobin decreased <13 (Male) or <12 (Female) to >=10 <10 to >=8 <8 Hemoglobin increased >16 (Male) or >15 (Female) to <=18 >18
Platelets (10^9/L)	Platelets decreased 0 to <20 >=20 to <50 >=50 to <100 >=100 to <LLN Platelets increased >ULN
Neutrophil (10^9/L)	Neutrophil decreased >=0 to <0.5 >=0.5 to <1.0 >=1.0 to <1.5 >=0.5 to <LLN Neutrophil increased >ULN

Table 11-8 Threshold Analysis Criteria for Clinical Laboratory Tests

Parameter	Threshold Analysis Criteria
Lymphocyte (10^9/L)	Lymphocyte decreased <0.8 to >=0.5 <0.5 to >=0.2 <0.2 Lymphocyte increased >4 to >=20 >20
Leukocytes (10^9/L)	Leukocytes decreased <4.0 to >=3.0 <3.0 to >=2.0 <2.0 to >=1.0 <1.0 Leukocytes increased >100
Methemoglobin (%)	>ULN to <=5 >5 to <=10 >10
Monocytes (10^9/L)	>ULN <LLN
Nucleated Erythrocytes	>ULN <LLN
Reticulocyte (10^9/L)	>=100 <=20
Clinical Chemistry (LFT)	
ALT (U/L)	>ULN to <=3xULN >3x to <=5xULN >5x to <=8xULN >8x to <=20xULN >20xULN >3xULN >5xULN >8xULN
AST (U/L)	>ULN to <=3xULN >3x to <=5xULN >5x to <=8xULN >8x to <=20xULN >20xULN >3xULN >5xULN >8xULN

Table 11-8 Threshold Analysis Criteria for Clinical Laboratory Tests

Parameter	Threshold Analysis Criteria
ALT (U/L) or AST (U/L)	(ALT>ULN to <=3xULN) or (AST>ULN to <=3xULN) (ALT>3x to <=5xULN) or (AST>3x to <=5xULN) (ALT>5x to <=8xULN) or (AST>5x to <=8xULN) (ALT>8x to <=20xULN) or (AST>8x to <=20xULN) (ALT>20xULN) or (AST>20xULN) (ALT>3xULN) or (AST>3xULN) (ALT>5xULN) or (AST>5xULN) (ALT>8xULN) or (AST>8xULN)
ALP (U/L)	>ULN to <=1.5xULN >1.5x to <=2.5xULN >2.5x to <=5xULN >5x to <=20xULN >20xULN
Total bilirubin (umol/L)	>=34.2 >ULN to <=1.5xULN >1.5x to <=2xULN >2x to <=3xULN >3x to <=10xULN >10xULN
Direct bilirubin (umol/L)	>ULN to <=1.5xULN >1.5x to <=2xULN >2x to <=3xULN >3x to <=10xULN >10xULN
ALT (U/L) and total bilirubin (umol/L)	Total bilirubin >2xULN within ± 30 days of ALT>3xULN
AST (U/L) and total bilirubin (umol/L)	Total bilirubin >2xULN within ± 30 days of AST>3xULN
(ALT (U/L) or AST (U/L)) and total bilirubin (umol/L)	Total bilirubin >2xULN within ± 30 days of (ALT>3xULN or AST>3xULN)
Clinical Chemistry (NON-LFT)	
Albumin (g/L)	<35 to >=30 <30 to >=20 <20
Creatinine (umol/L)	>ULN to <=1.5xULN >1.5x to <=3xULN >3x to <=6xULN >6xULN
Protein (g/L)	>ULN <LLN
Urea nitrogen (mmol/L)	>ULN to <=1.5xULN >1.5x to <=3xULN >3x to <=6xULN >6xULN

Table 11-8 Threshold Analysis Criteria for Clinical Laboratory Tests

Parameter	Threshold Analysis Criteria
Calcium (mmol/L)	Hypocalcemia <2.25 to >=2.0 <2.0 to >=1.75 <1.75 to >=1.5 <1.5 Hypercalcemia >2.5 to <=2.9 >2.9
Chloride (mmol/L)	>ULN <LLN
Magnesium (mmol/L)	Hypomagnesemia <0.6 to >=0.5 <0.5 to >=0.4 <0.4 to >=0.3 <0.3 Hypermagnesemia >1.00 to <=1.23 >1.23 to <=3.30 >3.30
Potassium (mmol/L)	Hypokalemia <3.5 to >=3.0 <3.0 to >=2.5 <2.5 Hyperkalemia >5.0 to <=5.5 >5.5 to <=6.0 >6.0 to <=7.0 >7.0
Sodium (mmol/L)	Hyponatremia <135 to >=130 <130 to >=120 <120 Hypernatremia >145 to <=150 >150 to <=155 >155 to <=160 >160
Phosphorus (mmol/L)	Hypophosphatemia <0.74 to >=0.6 <0.6 to >=0.3 <0.3 Hyperphosphatemia >1.5

Table 11-8 Threshold Analysis Criteria for Clinical Laboratory Tests

Parameter	Threshold Analysis Criteria
Glucose (mmol/L)	Hypoglycemia <4.0 to >=3.0 <3.0 to >=2.2 <2.2 to >=1.7 <1.7 Hyperglycemia >7.9 to <=8.9 >8.9 to <=13.9 >13.9 to <=27.8 >27.8
Coagulation	
Activated partial thromboplastin time (sec)	>ULN to <=1.5xULN >1.5 to <=2.5xULN >2.5xULN
Prothrombin time (sec)	>ULN to <=1.5xULN >1.5 to <=2.5xULN >2.5xULN
Prothrombin time international normalized ratio (ratio)	>ULN to <=1.5 >1.5 to <=2.5 >2.5
Immunology	
CD4 Lymphocyte (10^6/L)	>=500 <500 to >=200 <200 to >=50 <50

Table 11-9 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis Criteria
Heart Rate (beats/min)	Bradycardia <50 to >=45 <45 >=10 to <20 decrease from baseline >=20 decrease from baseline <50 and >=10 to <20 decrease from baseline <50 and >=20 decrease from baseline Tachycardia >100 to <=115 >115 to <=130 >130 >=10 to <20 increase from baseline >= 20 increase from baseline >100 and >=10 to <20 increase from baseline >100 and >=20 increase from baseline
PR Interval (msec)	>=240 to <300 >=300 >=200 and >=40 to <100 increase from baseline >=200 and >=100 increase from baseline
QRS Interval (msec)	>110 to <=160 >160 >=20 to <40 Increase from baseline >40 Increase from baseline
QTcF Interval (msec)	>450 to <500 (male) or >470 to <500 (female) >=500 >10 to <=20 increase from baseline >20 to <=40 increase from baseline >40 to <=60 increase from baseline >60 increase from baseline

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis Criteria
Pulse rate (beats/min)	Bradycardia <50 to >=45 <45 >=10 to <20 decrease from baseline >=20 decrease from baseline <50 and >=10 to <20 decrease from baseline <50 and >=20 decrease from baseline Tachycardia >100 to <=115 >115 to <=130 >130 >=10 to <20 increase from baseline >=20 increase from baseline >100 and >=10 to <20 increase from baseline >100 and >=20 increase from baseline
SBP (mmHg)	SBP increased >140 to <=160 >160 >10 to <=20 increase from baseline >20 increase from baseline >140 to <=160 and >10 to <=20 increase from baseline >140 to <=160 and >20 increase from baseline >160 and >10 to <=20 increase from baseline >160 and >20 increase from baseline SBP decreased <90 to >=80 <80 >10 to <=20 decrease from baseline >20 decrease from baseline <90 to >=80 and >10 to <=20 decrease from baseline <90 to >=80 and >20 decrease from baseline <80 and >10 to <=20 decrease from baseline <80 and >20 decrease from baseline

Table 11-10 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis Criteria
DBP (mmHg)	DBP increased >90 to <=100 >100 >5 to <=10 increase from baseline >10 increase from baseline >90 to <=100 and >5 to <=10 increase from baseline >90 to <=100 and >10 increase from baseline >100 and >5 to <=10 increase from baseline >100 and >10 increase from baseline DBP decreased <60 to >=45 <45 >5 to <=10 decrease from baseline >10 decrease from baseline <60 to >= 45 and >5 to <=10 decrease from baseline <60 to >= 45 and >10 decrease from baseline <45 and >5 to <=10 decrease from baseline <45 and >10 decrease from baseline