STATISTICAL ANALYSIS PLAN

A Phase 3 Study of Lenti-D Drug Product after Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects ≤ 17 Years of Age with Cerebral Adrenoleukodystrophy (CALD)
Protocol ALD-104

Protocol Number:	ALD-104
Protocol Version and Date:	Version 8.0: 22 November 2022
Name of Test Drug:	Elivaldogene autotemcel (also known as Lenti-D Drug Product)
Phase:	Phase 3
Methodology:	Single arm, multi-site study
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Analysis Plan Date:	14 September 2023
Analysis Plan Version:	5.0
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APPROVAL OF THE STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

Title: A Phase 3 Study of Lenti-D Drug Product after Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects ≤ 17 Years of Age with Cerebral Adrenoleukodystrophy (CALD)

Sponsor Approval:

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABCD1	ATP-binding cassette, sub-family D, member 1
AE	Adverse event
ALD	Adrenoleukodystrophy
ALDP	Adrenoleukodystrophy protein
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ANC	Absolute neutrophil count
BMI	Body mass index
BQL	Below quantitation limit
BRIEF	Behavior Rating Inventory of Executive Function
CALD	Cerebral adrenoleukodystrophy
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLC	Day of last contact
DMC	Data monitoring committee
EOI	Events of interest
EOS	End of Study

Abbreviation	Definition
FSIQ	Full-Scale Intelligence Quotient
GdE	Gadolinium enhancement
GVHD	Graft-versus-host disease
HSC(s)	Hematopoietic stem cell(s)
HSCT	Hematopoietic stem cell transplant
ICF	Informed consent form
ICH	International Conference on Harmonization
ITT	Intent-to-treat
IV	Intravenous
ICU	Intensive care unit
IS	Insertion site
ISA	Integration site analysis
LLN	Lower limit of normal
LVV	Lentiviral vector
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Major functional disability
MRI	Magnetic resonance imaging

Abbreviation	Definition
NE	Neutrophil Engraftment
NEP	Successful Neutrophil Engraftment Population
NFS	Neurologic Function Score
PCS	Potentially Clinically Significant
PE	Platelet engraftment
PedsQL	Pediatric Quality of Life Inventory
PIQ	Performance Intelligence Quotient
PT	Preferred Term
RCL	Replication competent lentivirus
Rel Day	Relative Study Day
Rel Month	Relative Month
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SI	International System of Units
SOE	Schedule of Events

Abbreviation	Definition
SOC	System Organ Class
TP	Transplant Population
TRNE	Transplantation to neutrophil engraftment
ULN	Upper limit of normal
US	United States
VABS	Vineland Adaptive Behavior Scales
VCN	Vector copy number
VIQ	Verbal Intelligence Quotient
VLCFA	Very long chain fatty acids

1. INTRODUCTION

1.1. Objectives of Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to meet the objectives of Study ALD104, which are to evaluate the efficacy and safety of elivaldogene autotemcel (also known as Lenti-D Drug Product, hereafter referred to as eli-cel) after myeloablative conditioning with busulfan and fludarabine in subjects with CALD. This SAP is based on Protocol ALD-104 v8.0, dated 22 November 2022.

The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the ALD-104 clinical study report (CSR). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described.

1.2. Synopsis of Study Design

Study ALD-104 is an international, non-randomized, open-label, multi-site study in male subjects with CALD (≤ 17 years of age at enrollment). Approximately 35 subjects will be infused with eli-cel after myeloablative conditioning with busulfan and fludarabine.

The study objectives are to evaluate the efficacy and safety of eli-cel after myeloablative

conditioning with busulfan and fludarabine in subjects with CALD.

Study endpoints are described in Section 2.2 of the ALD-104 protocol and listed in Section 1.3 of this SAP. The efficacy and safety assessment schedules are detailed in Section 6.1 of the protocol.

For each subject, the study procedures can be summarized as follows:

- Screening (assessment for eligibility)
- Enrollment: met eligibility criteria, based on screening assessments
- Mobilization and Apheresis
- Confirmation of continued eligibility before conditioning
- Conditioning and Washout
- Eli-cel infusion
- Maintenance (Follow-up) to Month 24

1.2.1. Screening and Enrollment

Once subjects have provided informed consent and met inclusion/exclusion criteria, they will be considered enrolled in the study.

1.2.2. Mobilization, Apheresis, Conditioning, and Study Treatment

Enrolled subjects will undergo HSC mobilization mediated by G-CSF and plerixafor and harvest by apheresis using institutional practice treatment guidelines. G-CSF is defined for this protocol to mean either filgrastim or lenograstim. The harvested cells will be selected for the CD34+ marker to enrich for HSC, transduced with eli-cel lentiviral vector (LVV), stored frozen in cryopreservation solution while aliquots are being tested to ensure they meet product quality specifications, and returned by IV infusion through a central venous catheter to the same subject after the subject is myeloablated and lymphodepleted with busulfan IV and fludarabine IV. The subject will only undergo myeloablation after the transduced cells are released for clinical use and the drug product is at the clinical site.

Re-confirmation of the subject's eligibility will be done prior to the start of conditioning.

1.2.3. Follow-up

All subjects will be followed for 24 months post eli-cel infusion under the ALD-104 protocol. Then, subjects are expected to be followed for an additional 13 years under a separate follow-up protocol (LTF-304). The 13-year follow-up study will focus on long-term safety, with an emphasis on integration site analysis (ISA) and long-term efficacy to evaluate durability of response.

1.2.4. Data Monitoring Committee

An independent DMC composed of members with appropriate scientific and medical expertise to monitor the study will be convened before the study is opened. A charter describing the composition and conduct of the DMC will be drafted by the Sponsor and agreed to by all DMC members prior to the DMC's initial meeting. The DMC will meet by teleconference for scheduled meetings biannually and ad hoc as circumstances require. In addition, the DMC will review hematologic and ISA data on a quarterly basis. The DMC will have the right to recommend halting the study at any time due to concerns for the safety of the participants.

1.3. Efficacy, Safety, and Exploratory Endpoints

The efficacy, safety, and exploratory endpoints are listed below from the study protocol Section 3.2. Detailed definitions and analysis methods of the endpoints are provided in Section 4 of this SAP.

1.3.1. Efficacy Endpoints

The primary efficacy endpoint is:

- Proportion of subjects who are alive and have none of the 6 major functional disabilities (MFDs) at Month 24 (i.e. Month 24 MFD-free survival). MFDs are defined as follows:
  - loss of communication
  - cortical blindness
  - tube feeding
  - total incontinence
  - wheelchair dependence
  - complete loss of voluntary movement

These MFDs have been characterized as having the most significant impact on a patient's ability to function independently, and represent unambiguous and profound neurologic functional categories indicating end-stage disease (Miller et al., 2016). The inclusion criteria limiting eligibility to patients with early-stage disease will prohibit patients from entering the trial with a pre-existing MFD.

In addition to experiencing any MFDs or death, the following events will also be considered as a failure to meet the primary efficacy endpoint: requirement for rescue cell administration or an allogeneic hematopoietic stem cell transplantation (allo-HSCT), withdrawal from study, or lost to follow-up by Month 24. See also Section 4.2.2.

Secondary efficacy endpoints are the following:

- Proportion of subjects without gadolinium enhancement on MRI (i.e., GdE-) at Month 24
- Value and change in total NFS from Baseline to protocol scheduled visits
- MFD-free survival over time
- Overall survival
- Detectable vector copy number (VCN) in peripheral blood cells by Month 6

1.3.2. Safety Endpoints

The primary safety endpoint is:

- The proportion of subjects with neutrophil engraftment after drug product infusion

The secondary safety endpoints are:

- The proportion of subjects who experience either acute (≥ Grade II) or chronic Graft-versus-host disease (GVHD) by Month 24
- Time to neutrophil engraftment after drug product infusion
- The proportion of subjects with platelet engraftment by Month 24
- Time to platelet engraftment post-drug product infusion
- The proportion of subjects with loss of neutrophil engraftment post-drug product infusion by Month 24
- The proportion of subjects who undergo a subsequent HSC infusion by Month 24
- The proportion of subjects who experience transplant-related mortality through 100 and 365 days post-drug product infusion
- Proportion of subjects with clinical ≥ Grade 3 AEs, all drug product-related AEs, all SAEs, ≥ Grade 3 infections, and clinically significant changes in laboratory parameters by Month 24
- The proportion of subjects who experience ≥ Grade II acute GVHD by Month 24
- The proportion of subjects who experience chronic GVHD by Month 24
- Number of emergency room visits (post-neutrophil engraftment) by Month 24
- Number and duration of in-patient hospitalizations (post-neutrophil engraftment) by Month 24
- Number and duration of ICU stays (post-neutrophil engraftment) by Month 24
- The number of subjects in which vector-derived RCL is detected by Month 24
- The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.) by Month 24

Note: transplant-related mortality as determined by the Investigator; severity of AEs as assessed by the Investigator as described in study protocol Section 6.6.2 ; acute GVHD graded on the Acute GVHD Grading Scale (I-IV); chronic GVHD as determined by the Investigator.


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2. SUBJECT POPULATIONS

2.1. Analysis Populations

Three populations will be evaluated in efficacy, safety, and exploratory analyses.

The Intent-to-treat Population (**ITT**) will consist of subjects who initiate any study procedures, beginning with mobilization by G-CSF. This population will be used for the analyses of selected safety endpoints and for the supportive analysis of the primary efficacy endpoint (specified in Section 4), if it is different from the Transplant Population (TP).

The Transplant Population (**TP**) will consist of subjects who receive eli-cel. This analysis population will be used for the analyses of all efficacy endpoints and selected safety endpoints.

The Successful Neutrophil Engraftment Population (**NEP**) will consist of subjects who received eli-cel and achieved neutrophil engraftment defined as having 3 consecutive absolute neutrophil count (ANC) laboratory values of $\geq 0.5 \times 10^9$ cells/L (after initial post-infusion nadir) obtained on different days by 42 days post-infusion of eli-cel. The NEP will be used for the supportive analysis of the primary efficacy endpoint as well as for selected efficacy and safety endpoints as specified in Section 4, if it is different from the TP.

2.2. Protocol Deviations

Categorization of protocol deviations into major/minor deviations will be determined prior to database lock, by a review of the protocol deviation data collected on the case report form (CRF).

All protocol deviations will be presented in a data listing, including the categorization of major or minor.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Estimation

The number of subjects planned to be infused with eli-cel is approximately 35.

The sample size of 35 subjects will provide a 95% two-sided exact confidence interval (CI) for the estimated MFD-free survival rate that is at most 34.6% wide (dependent on the observed MFD-free survival rate). If 17 out of 35 subjects are MFD-free, the exact 95% CI will be (31.4%, 66.0%) with a width of 34.6%; if 26 out of 35 subjects are MFD-free, the exact 95% CI will be (56.7%, 87.5%) with a width of 30.8%. This sample size is appropriate for nominal comparisons with other CALD studies.

3.2. General Methods

Statistical methods will be primarily descriptive in nature and will include point estimates and confidence limits as appropriate.

All relevant data collected within this study, as well as derived data used in efficacy and safety analyses, will be presented in subject-level listings.

Descriptive summary statistics will be tabulated for key data:

- For categorical variables, the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, along with the exact 2-sided 95% confidence interval (CI) as appropriate. The exact CIs will be obtained using the Clopper-Pearson method (Agresti 2001).
- For continuous variables, the number of observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum values will be presented, along with the 2-sided 95% CI of the mean as appropriate.
- For time-to-event variables, the Kaplan-Meier method will be used, as specified in Section 4.2.3.1.

Figures may be presented in addition to subject listings and summary tables as appropriate.

If a subject in the TP undergoes a second allo-HSCT, additional analysis will be conducted with

the study divided into the following study periods if sample size is enough:

Study Period	Safety and Pharmacodynamic Endpoints
Eli-cel Period	This period begins from day of eli-cel infusion (Rel Day 1) up to the day before initiation of conditioning for the allo-HSCT. For subjects who don't undergo conditioning prior to allo-HSCT, the day before allo-HSCT will be used. For subjects who don't have allo, Eli-cel period begins from day of eli-cel infusion (Rel Day 1) up to the day of last contact (DLC).
allo-HSCT Period	This period begins from day of initiation of conditioning for allo-HSCT up to DLC). For subjects who don't undergo conditioning prior to allo-HSCT, the day before allo-HSCT will be used.

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

3.3. Computing Environment

All planned statistical analyses and data summarizations will be performed using SAS statistical software Version 9.3 or higher, unless otherwise noted.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or above. It is noted that coding of AEs may need to be updated based on the time of the analysis.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Version Global B3 March 2021 or above depend on the time of analysis.

3.4. Relative Days and Baseline Definitions

The day of eli-cel infusion is designated as Relative Study Day 1 (Rel Day 1). Pre-treatment and on-treatment days are numbered relative to Rel Day 1. The preceding day is Rel Day -1, the day before that is Rel Day -2, etc. All data listings that contain an evaluation date will also contain the corresponding Rel Day. This definition of Rel Day 1 is CDISC compliant and is used for all data analyses. Relative Month (Rel Month) may also be displayed where appropriate and will be calculated as Rel Month=Rel Day/30.4375.

For efficacy endpoints and the exploratory endpoints as appropriate , baseline is defined as the non-missing assessment closest but prior to conditioning.

For safety endpoints, all laboratory data including vital signs, echo- and electro-cardiograms, baseline is defined to be the non-missing assessment closest but prior to mobilization.

3.5. Analysis Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as designated on the CRF even if the assessment is outside of the visit window. If the evaluation visit is not available in the database but there is data from an unscheduled visit that is inside a visit window as defined in Table 1, Table 2 below, the data from the unscheduled visit will be used for the visit in data summaries. For subjects with multiple unscheduled evaluations within a visit window, the evaluation closest to the target visit date will be used. In case of evaluations equidistant to the target visit date within a visit window, results of the later evaluation will be used. This applies to all assessments without designated visits.

Table 1: Analysis Visit Windows for Assessments without Designated Visits

	Follow-Up Visit							
	Week 2	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 16**
Target Rel Day (D)	D16	D31	D61	D91	D181	D271	D361	D481
	Visit Window: First Day - Last Day							
Clinical chemistry Vital signs	D2-23	D24-45	D46-75	D76-135	D136-270		D271-420	D421-540
ALDP		D2-45	D46-75	D76-135	D136- 270		D271-420	D421-540
VCN		D2-45	D46-75	D76-135	D136-225	D226-315	D316-420	D421-540
VLCFA							D2-540	
Bone marrow core needle biopsy and aspirate (ISA, VCN and Storage) Hematopathology review of peripheral blood smear					D2-270		D271-DLC	

NFS Neurological exam	D2-23	D24-60		D61-135	D136-270		D271-450	
Neuropsychological tests Global assessment							D2-540	
PedsQL				D2-135	D136-270		D271-540	
MRI					D2-270		D271-450	
ISA					D2-225	D226-315	D316-420	D421-540

	Follow-Up Visit		
	Month 18	**Month 20**	**Month 24**
Target Rel Day (D)	D541	D601	D721
	Visit Window: First Day - Last Day		
Clinical chemistry Vital signs		D541-660	D661-DLC
ALDP		D541-660	D661-DLC
VCN		D541-660	D661-DLC
VLCFA			D541-DLC
Bone marrow core needle biopsy and aspirate (ISA, VCN and Storage)			
NFS Neurological exam	D451-630		D631-DLC

Neuropsychological tests Global assessment			D541-DLC
PedsQL			D541-DLC
MRI	D451-630		D631-DLC
ISA		D541-660	D661-DLC

Note: DLC = Day of Last Contact.

Note: As of ALD-104 Protocol V4.0, Month 9, Month 15 and Month 21 are no longer required scheduled visits. Data that is available at these three visits will not be used in data summaries but still shown in data listings.

Table 2: Analysis Visit Windows for Hematology

Visit	Target Rel Day (D)	Analysis Window: First Day - Last Day
Week 2	D16	D2-23
Month 1	D31	D24-45
Month 2	D61	D46 - 75
Month 3	D91	D76 - 105
Month 4	D121	D106 - 135
Month 5	D151	D136 - 165
Month 6	D181	D166 - 181
Month 7	D211	D182 - 225
Month 8	D241	D226 - 255
Month 9	D271	D256 - 285
Month 10	D301	D286 - 315
Month 11	D331	D316 - 345

Month 12	D361	D346 - 375
Month 16	D481	D376 - 540
Month 20	D601	D541 - 660
Month 24	D721	D661 - DLC

3.6. Study Periods for AEs and Concomitant Medications

For each subject, the study will be designated to one or more of the following Study Periods:

- ICF to <M: day of signed ICF to before initiation of mobilization
- M to <C: initiation of mobilization until before initiation of conditioning
- C to <NE: initiation of conditioning until the day before neutrophil engraftment (NE) (for subjects who didn't achieve NE and discontinue from study, the end of this Study Period is DLC or End of Study (EOS))
- NE to M12: day of NE to Rel Day 365 (subjects who didn't achieve NE will not be included in this study period)
- >M12 to M24: >12 months post eli-cel infusion (Rel Day 366) to DLC (subjects who do not achieve NE will not be included in this study period)
- D1 to M24: Rel Day 1 (date/time of eli-cel infusion) to DLC

Each adverse event (AE) will be designated to one of the study periods based on the AE start date/time. If an AE started in one period and continues into the next period, it will be counted only in the first period. However, if an AE starts and ends in one period and recurs in the next period, it will be counted in both periods. For AEs with worsening severity in which the AE starts in the first period and worsens in the next period, the subject will be counted in both periods.

Each concomitant medication will be associated with the study period(s) based on subject exposure during each period, thus it is possible for a concomitant medication to be associated with more than one study period.

For AEs and laboratory assessments, to determine the boundaries involving mobilization (M), conditioning (C), and eli-cel infusion (Rel Day 1), the date and time of the events involved (mobilization, conditioning, eli-cel infusion, start of AE, time of laboratory assessment) will be used if available (if time is not available only the date will be used). For the boundaries of the other study periods and for concomitant medications, only dates will be used.

Additionally, AE summary tables will also present AEs in each of the following periods based on the AE start date/time:

- NE to M24: day of NE to DLC (subjects who didn't achieve NE will not be included in this study period)

- D1 to M12: Rel Day 1 (date/time of eli-cel infusion) through 12 months post eli-cel infusion (Rel Day 365)
- D1 to M24: Rel Day 1 (date/time of eli-cel infusion) to DLC
- ICF to M24: day of signed ICF to DLC
- >M12 to M24: >12 months post eli-cel infusion (Rel Day 366) to DLC (subjects who do not achieve NE will not be included in this study period)

Concomitant medication summary tables will also present in the following period:

- ICF to M24: day of signed ICF to DLC

G-CSF usage summary table will also present in the following period:

- D1 to M12: Rel Day 1 (date/time of eli-cel infusion) through 12 months post eli-cel infusion (Rel Day 365)
- D1 to M24: Rel Day 1 (date/time of eli-cel infusion) to DLC
- ICF to M24: day of signed ICF to DLC
- >M12 to M24: >12 months post eli-cel infusion (Rel Day 366) to DLC (subjects who do not achieve NE will not be included in this study period)

3.7. Missing Data and Imputations

In general, there will be no substitutions made to accommodate missing data points. Subjects who discontinue prior to the Month 24 visit will be considered treatment failures in the primary efficacy analysis.

For the purpose of designating AEs and concomitant medications to study periods, partial start dates will be handled as follows:

- If the day of the month is missing, the start day will be set to the first day of the month.
  - Exception for AE start date: if the AE start month and year is the same month and year as eli-cel infusion, in order to conservatively report the event as treatment-emergent, the start date will be set to the date of eli-cel infusion, except in cases where this will lead to a start date being after end date. In these situations, the original rule will be applied.
- If the day and month are both missing, the day and month will be assumed to be January 1.

- Exception for AE start date: if the AE starts in the same year as eli-cel infusion, in order to conservatively report the event as treatment-emergent, the start date will be set to the date of eli-cel infusion, except in cases where this will lead to a start date being after end date. In these situations, the original rule will be applied.

- If the date is completely missing:
  - The AE start date will be set to the date of eli-cel infusion, except when this would lead to a start date being after the end date. In these situations, the start date will be set to the first day of the month of the AE end date.
  - The concomitant medication start date will be set to the day before mobilization, except when this would lead to a start date being after the end date. In these situations, the start date will be set to the first day of the month of the medication end date.

For AEs and concomitant medications, partial end dates will be handled as follows:

- If the day of the month is missing, it will be set to the last day of the month or the DLC, whichever occurs first.
- If both the day and the month are missing, it will be set to December 31 or the DLC, whichever occurs first.
- If the end date is completely missing, no imputation will be implemented.

Partial dates for diagnosis of CALD will be imputed as follows: if the day of the month is missing, the diagnosis day will be set to the first day of the month; if the day and month are both missing, the diagnosis day and month will be set to January 1. If this leads to diagnosis date earlier than birth date, then the diagnosis date will be set to birth date.

Partial birth dates will be imputed as follows: if the day of the month is missing, the birth date will be set to the first day of the month; if the day and month are both missing, the birth date will be set to January 1.

For the purpose of calculating the duration of in-patient hospitalization, missing admission/discharge date of in-patient hospitalization will be imputed as:

- If only day is missing: for discharge date, impute it as the last day of that month, or DLC, whichever occurs first; for admission date, impute it as the 1st of month, or associated SAE start date if hospitalization reason is SAE, whichever occurs later.
- If month and day are both missing: for discharge date, impute it as December 31, or DLC, whichever occurs first; for admission date, impute to January 1, or associated SAE start date if hospitalization reason is SAE, whichever occurs later.
- If the date is completely missing: the day of admission will be set to associated SAE start date if hospitalization reason is SAE; the day of discharge will be set to the DLC.

3.8. Adjustment for Covariates

No adjustment for covariates is planned for analysis of this study. Impact of covariates will be explored in analyses of pooled data from this study with other studies on CALD.

3.9. Multiple Comparisons / Multiplicity

No multiplicity adjustment will be made in the analyses of efficacy and safety endpoints in this study.

3.10. Withdrawals, Dropouts, Lost to Follow-up

Subjects who withdraw or discontinue from the study after mobilization will not be replaced.

3.11. Planned Analysis

Planned analyses for this study include the following:

- Interim analyses are planned in support of regulatory submissions. The timing of these analyses and the number of subjects included in each analysis will take into account specific requests from regulatory agencies and applicable regulatory guidance.
- A final analysis will be performed when all subjects treated with eli-cel complete the study.

Safety data are reviewed on an ongoing basis for signal detection and to support preparation of regulatory submission documents. Analyses of study data may also be performed for the purposes of internal data review, data monitoring committee (DMC), preparing for regulatory meetings, and updating the scientific community. All analyses will utilize the same analysis methods outlined in this SAP.

3.12. COVID-19 Impact Analysis

Due to the COVID-19 pandemic, subjects may not be able to attend normal study visits. If a visit is missed due to COVID-19 reasons (e.g. unable to fly, unwilling to travel, family or subject affected by COVID-19, hospital closure, etc.), the subject may be able to complete study assessments at a facility that is closer to his home or virtually (e.g., via electronic video methods) with the enrolling center. All the M24/EOS Visits delayed due to COVID-19, will still be

collected as M24 Visits. Data will be collected for COVID-19 impact on attending normal study visits.

A listing of COVID-19 related protocol deviations will be provided.

Analyses will be performed to measure the effect of disruptions due to the pandemic on these assessments:

- Descriptive summary of COVID-19 impact on this study when applicable:
    - The analysis will tabulate number and percent of missed, out of window and altered/virtual study visits, and early termination of the study due to the effects of the COVID-19 Public Health Emergency.
    - Mean, median, and range of days of delayed post infusion visits.
    - Incidence of COVID-19, and related events, such as death, etc.

For the primary and secondary efficacy and safety endpoint analyses, in general, COVID-19 related missing data are considered as missing completely at random (MCAR). Therefore, same approaches for treating missing data and imputations as laid out in Section 3.7 applies, i.e., the primary analyses will be based on available observed data, and use the same methods as specified in Section 4.2 and Section 4.2.4.

Besides the primary analyses, if applicable, the following sensitivity analyses may be conducted:

- For continuous variable endpoints, missing data patterns will be summarized. Approaches to missing data will be explored, and the methods potentially chosen will be dependent on the patterns observed.
- For the proportion based endpoints, LOCF approach will be used.

4. STUDY ANALYSES

4.1. Study Information

4.1.1. Overview of Study Information

The following subsections provide details on the analyses of subject disposition, analysis populations, and baseline and treatment data. Table 3 is a summary of analysis populations to be used. Note that analyses based on the ITT population and NEP will only be performed if they are different from the TP.

Table 3: Analyses of Study Information

	Analysis Population
Subject disposition	ITT
Analysis Populations	ITT
Demographics and baseline disease characteristics	ITT TP NEP
Mobilization and apheresis	ITT
Conditioning	TP
Eli-cel infusion	TP NEP

4.1.2. Disposition

A tabulation of all screened subjects will be included to show the number of subjects screened, the number of screen failures, the number of subjects enrolled, and the number of subjects in the ITT population.

A tabulation of the disposition of subjects in the ALD104 study ITT population will be presented overall and by investigational site, for the following:

- Number and percent of subjects who initiated mobilization
- Number and percent of subjects who initiated conditioning
- Number and percent of subjects who were infused with eli-cel
- Number and percent of subjects who discontinued study, and reason for discontinuation
- Number and percent of subjects who completed study, and subjects who will participate in the long-term follow-up study LTF-304
- Number and percent of subjects who are in study at the time of data cut
- Descriptive statistics for the duration of follow-up for subjects who were infused with eli-cel
- Subject-years of follow-up, which is the sum over all subjects' duration of follow-up
- The number of subjects receiving allo-HSCT, and the reason for receiving allo-HSCT during the study.

Additionally, the numbers and percentages of the last and cumulative study visit that subjects in the TP completed will be tabulated. A tabulation of enrollment by site number and site country will also be presented.

A subject listing of screen failures with reasons will be presented.

4.1.3. Analysis Populations

The number and percent of subjects (out of the ITT Population) in each analysis population defined in Section 2.1 will be tabulated.

4.1.4. Demographics and Baseline Disease Characteristics

The following demographic and baseline characteristic factors will be summarized:

- Age at CALD diagnosis (years)
- Age and age category (<2, ≥2 to <6, ≥6 to <12, and ≥12 to <18) at informed consent (years)
- Age at eli-cel infusion (years)
- Weight at screening (kg)

- Height at screening (m)
- Body mass index (BMI) at screening (kg/m^2)
- Sex
- Country of origin
- Race and ethnicity
- Method of diagnosis of ALD/CALD
- Signs and symptoms of ALD/CALD
- Availability of matched sibling donor
- NFS at Baseline
- Loes score and Loes pattern at Baseline
- Number of prior gadolinium scans
- Time from CALD diagnosis to eli-cel infusion (months)
- Time from informed consent to eli-cel infusion (days)
- Presence of any significant co-morbid conditions (defined as any ongoing medical history)

4.1.5. Mobilization, Apheresis, and Conditioning Details

Descriptive statistics will be presented for the following information on mobilization:

- Number of mobilization cycles per subject
- Average daily dose of G-CSF (µg/kg/day) and plerixafor (mg/kg/day)
- Amount of G-CSF (µg/kg) and plerixafor (mg/kg) used per subject per cycle
- Number of days of G-CSF administered and number of days of plerixafor administered during mobilization

Descriptive statistics will be presented for the following information on apheresis:

- Number of apheresis procedures performed per mobilization cycle
- Average daily peripheral CD34+ count (cells/µL) during mobilization
- Total blood volume processed during apheresis (mL)
- Total number of nucleated cells collected (cells × 10^8)
- Total number of CD34+ cells collected (cells × 10^6/kg)
- Average number of CD34+ cells collected per day (cells × 10^6/kg)
- Total number of CD34+ cells sent for transduction (cells × 10^6/kg)
- Total number of CD34+ cells stored for rescue (cells × 10^6/kg)

Descriptive statistics will be presented for the following information on conditioning:

- Average daily dose of busulfan (mg/kg/day)
- Estimated average daily AUC (µM*min) for busulfan
- Total dose of fludarabine (mg/m^2)

Estimated average daily AUC for busulfan is calculated as the average of the observed and imputed AUC. If a subject has a missing value of AUC, it is imputed to the product of the dose on that day and the mean of the ratios of the observed AUC and the corresponding doses.

4.1.6. Eli-cel Infusion

Descriptive statistics will be presented for the following information on eli-cel infusion:

- Subjects' body weight at infusion (kg)
- VCN of eli-cel (eli-cel VCN; c/dg)
- Eli-cel total cell dose (CD34+ cells × 106 /kg)

- Number and percent of subjects that received rescue cells
- Percent lentiviral vector positive cells in eli-cel (DP %LVV+ Cells)
- %ALDP+ cells in eli-cel
- Vector copies per transduced cell (eli-cel VCN divided by DP %LVV+ Cells)

If a subject had multiple lots of eli-cel, the weighted average of eli-cel VCN, DP %LVV+ Cells, %ALDP+ cells and vector copies per transduced cell using the fractions of cell dose (dose per lot/total dose of all lots) as the weight will be derived per subject. Summary of subset of population might be presented as appropriate.

4.2. Efficacy Analysis

4.2.1. Overview of Efficacy Analyses

Statistical methods will generally consist of descriptive statistics and exact 2-sided 95% CI. The TP (defined in Section 2.1) will be used in the analyses of all efficacy endpoints. For the primary efficacy endpoint, the ITT will be used as a supportive analysis if it is different from the TP. The NEP will also be used as a supportive analysis if it is different from the TP.

4.2.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who have success in Month-24 MFD-free survival, which is a binary endpoint. To be considered a success for the primary endpoint, a subject must meet all following criteria:

1. Be alive at 24 months post infusion
2. Have not developed any of the MFDs (defined in Section 1.3.1) by 24 months post infusion
3. Have not received rescue cell administration or allo-HSCT by 24 months post infusion
4. Have not withdrawn from the study or been lost to follow-up by 24 months post infusion

For the primary analysis, the number and percent of subjects who achieve Month 24 MFD-free survival will be presented with the exact 95% CI for the TP. Failures of Month-24 MFD-free survival include failures that occur before EOS.

The ITT will be used as a supportive analysis if it is different from the TP. The NEP will also be used as a supportive analysis if it is different from the TP.

Analysis of this endpoint will be based on evaluable subjects for MFD-free survival in TP, defined as subjects who have been followed for 24 months (i.e. Rel Day of DLC ≥ 730) or have completed the Month 24 Visit or have discontinued from the study but would have been followed for 24 months if still on the study (i.e. Rel Day of data cut ≥ 730), at the time of the data cut.

Additionally, the number and percent of subjects with failure in each of the four MFD-free survival criteria will be presented in the following two ways:

a. Only the first of the failures for each subject will be counted, e.g., if a subject had multiple failures, only the failure which occurred first will be counted.

b. All of the failures for each subject will be counted, e.g., if a subject had multiple failures, all of the failures will be counted.

For a sensitivity analysis, failures for Month-24 MFD-free survival only include failures that occur on or before Rel Day 730. This sensitivity analysis will only be conducted when there is any failures for Month-24 MFD-free that occur after Rel Day 730.

For a second sensitivity analysis, failures for Month-24 MFD-free survival only include failures due to death or MFD. Evaluability of this sensitivity analysis is the same as primary analysis.

4.2.3. Secondary Efficacy Endpoints

Analyses of all secondary efficacy endpoints will be performed for the TP.

4.2.3.1. MFD-free Survival and Overall Survival Over Time

The time-to-event analysis of MFD-free survival and overall survival will be based on the Kaplan-Meier methodology. The 25th, 50th (median), and 75th percentiles will be presented with associated 2-sided 95% CIs. Event-free rates and 95% CIs at 12 and 24 months post eli-cel infusion (Rel Day 365 and 730, respectively), and the restricted mean survival time (RMST) along with the standard errors at 24 months post eli-cel infusion (Rel Day 730) will also be presented. The number and percent of events and censored observations will be provided. Kaplan-Meier plots of the survival function will be provided.

This analysis will be performed for the following secondary efficacy endpoints:

- MFD-free survival over time: Deaths, MFDs, and rescue cell administration or allo-HSCT are considered as events. If a subject did not experience any event, he will be censored at the DLC.

- A sensitivity analysis will be performed only considering deaths and MFDs as events. For subjects who are event free, if they discontinued from the study due to rescue cell administration or allo-HSCT, subjects will be censored at the day of rescue cell administration or allo-HSCT if not missing; otherwise he will be censored at the DLC.
- Overall survival: Deaths from any cause are considered as events. For subjects who are alive, they will be censored at the DLC.

Deaths will be presented in by-subject listings.

4.2.3.2. VCN in peripheral blood cells

Number and proportion of subjects who have detectable VCN in peripheral blood cells (PB VCN) values by Month 6 will be presented with the exact 95% CI. The proportion will be calculated based on subjects who had a VCN result (either detectable or undetectable) at Month 6.

Additionally, summary statistics of observed value will be presented by visit for PB VCN and VCN in CD14+ cells. Number and proportion of subjects who have detectable and undetectable levels of VCN will be tabulated at protocol specified assessment time points. The proportion will be calculated based on subjects who had a VCN result at the visit (either detectable or undetectable). VCN in bone marrow or other cell types will be presented in the listing if available and may be summarized when appropriate.

Box plot and by-subject plots over time will be presented for PB VCN and VCN in CD14+ cells values.

4.2.3.3. Resolution of Gadolinium Positivity on MRI

Note that contrast enhancement positive on MRI (GdE+) and contrast enhancement negative on MRI (GdE-) refer to any contrast positive or negative results. Gadolinium is the most frequently used contrast enhancement agent, so the term GdE is used throughout the analyses.

The number and percent of subjects who are GdE- at Month 24 will be provided with the exact 95% CI. The number and percent of subjects who are GdE+ and those who are GdE- will be provided by visit. The GdE status over time will be plotted by subject.

Sustained resolution of gadolinium positivity (sustained GdE-) is defined as having at least two consecutive GdE- results by MRI without a subsequent evaluation indicating gadolinium positivity. The number and percentage of subjects who achieve sustained GdE- by the Month 24 Visit will be provided with the exact 95% CI. The Rel Days from eli-cel infusion to the first occurrence of GdE- in the first sustained GdE- event will be descriptively summarized for subjects who achieve sustained GdE-.

For the endpoint GdE- at Month 24 and sustained GdE- at Month 24 above, evaluable subjects are defined as subjects who have completed the Month 24 GdE assessment.

4.2.3.4. Neurologic Function Score (NFS) and Loes Score

All MRIs will be assessed by a central reader(s), using the 34-point Loes scoring scale, which is widely used to diagnose and follow subjects with CALD. Loes patterns are also provided in data: "1" for Parietal-occipital, "2" for Frontal, "3" for Pyramidal tracts involvement, "4" for Cerebellar white matter involvement, and "5" for Combined parieto-occipital and frontal white matter involvement.

The NFS is a 25-point composite scale that assesses functional disabilities.

NFS, Loes Scores and Loes patterns, along with the changes from Baseline, will be summarized by visit. The NFS will be summarized as a categorical variable, while Loes scores will be summarized as a continuous variable.

Stable NFS is defined as maintaining an NFS ≤4 without an increase of >3 from Baseline. The number and percentage of subjects who achieve stable NFS at the Month 24 Visit will be provided along with the exact 95% CI.

Stable Loes score is defined as maintaining a Loes score ≤9 or not increasing by ≥6 from Baseline. The number and percentage of subjects who achieve stable Loes score at the Month 24 Visit will be provided along with the exact 95% CI.

For the endpoints stable NFS at Month 24 and stable Loes score at Month 24 above, evaluable subjects are defined as subjects who have non-missing Baseline and have completed the Month 24 assessment for the corresponding parameter.

NFS and Loes scores over time will be summarized by subject plot and box plot.

4.2.4. Exploratory Efficacy Endpoints

All exploratory endpoint analyses will be conducted based on TP except specified otherwise.

4.2.4.1. Specialty Laboratory Tests

- Summary statistics of observed value for percent of peripheral blood cells and CD14+ cells expressing adrenoleukodystrophy protein (ALDP) will be presented by visit.
- Bone marrow cells expressing ALDP will be presented in the listing if available, and may be summarized when appropriate.
- VCN in bone marrow will be presented in the listing, if available, and may be summarized when appropriate.

- Summary statistics of observed values, change from Baseline and percent change from Baseline for VLCFA levels in fasting serum: C26:0 LysoPC, C22:0, C24:0, C24:0/C22:0, C26:0 and C26:0/C22:0 will be presented by visit.

For specialty laboratory tests (e.g., %ALDP+ cells and VCN) with assessment values below quantitation limit (BQL), listings will report "BQL" for such values. For summary tables and figures, the BQL values will be set to 50% of the lower limit of quantification for the particular laboratory test. As a sensitivity analysis, summary will also be provided excluding all BQL values.

Box plot and by-subject plots over time will be presented for %ALDP+ cells and VCN values in peripheral blood and CD14+, if available.

Box plot and by-subject plot over time may be presented for VLCFA levels in fasting serum for C26:0 LysoPC, C26:0, and C26:0/C22:0.

Scatter plots (with the best-fitting line by linear regression using the least squares method) will be made to illustrate potential relationships between the following laboratory values. A Pearson correlation coefficient and p-value may be reported with the plot to serve for exploration purposes. Scatter plot will be made for the following:

- PB VCN at Month 6 vs. eli-cel VCN
- PB %ALDP+ cells at Month 6 vs. eli-cel VCN
- Estimated average daily busulfan AUC vs. ratio of PB VCN at Month 6/eli-cel VCN
- Median PB %ALDP+ cells vs. Median PB VCN across all visits
- Median CD14+ %ALDP+ cells vs. Median CD14+ VCN across all visits
- PB %ALDP+ cells at Month 6 vs. PB VCN at Month 6
- CD14+ %ALDP+ cells at Month 6 vs. CD14+ VCN at Month 6
- %Change from Baseline in VLCFA (C22:0, C24:0, C26:0 C24:0/C22:0, C26:0/C22:0, C26:0 LysoPC) vs. PB VCN at Month 12
- %Change from Baseline in VLCFA (C22:0, C24:0, C26:0 C24:0/C22:0, C26:0/C22:0, C26:0 LysoPC) vs. PB VCN at Month 24
- Eli-cel cell dose (total number of CD34+ cells/kg) vs. ratio of PB VCN at Month 6/eli-cel VCN
- Eli-cel %LVV+ cells vs. eli-cel VCN

- Eli-cel cell dose vs. Rel Day of neutrophil engraftment
- Eli-cel cell dose vs. Rel Day of platelet engraftment
- Eli-cel VCN vs. MFD-Free survival status at Month 24
- Eli-cel VCN vs. NFS change from Baseline at Month 24
- PB VCN at Month 24 vs. MFD-Free survival status at Month 24
- PB VCN at Month 24 vs. NFS change from Baseline at Month 24

4.2.4.2. Neuropsychological Tests

Full-Scale Intelligence Quotient (FSIQ) and selected sub-scores from Wechsler test will be summarized by visits and figures for both individual patient trends as well as for summary statistics may be produced.

All neuropsychological tests will be provided in listings.

4.2.4.3. Pediatric Quality of Life Inventory (PedsQL)

Subjects will be evaluated using Pediatric Quality of Life Inventory (PedsQL^{TM}) Measurement 4.0 Generic Core Scales at Pre-conditioning, and follow up Month 3, 6, 12, 24.

The questionnaires are specific to the age of subjects: 2-4 Yrs, 5-7 Yrs, 8-12 Yrs, 13-18 Yrs and 18-24 Yrs. Parents/caregiver are asked to evaluate their child in the following 4 dimensions for the past one month: Physical, Emotional, Social and School Functioning. The subjects may also be asked to evaluate for themselves in the following 4 dimensions for the past 1 month when appropriate: About My Health and Activities, About My Feeling, How I get Along with Others and About My Work/Studies, which correspond to physical, emotional, social and school functioning respectively. Within one dimension, each item is scored on a 5-point ordinal scale (0=Never, 1=Almost Never, 2=Sometimes, 3=Often, 4=Almost Always).

For ease of interpretability, items are reversed scored and linearly transformed to 0-100 scale (0 converted to100, 1 to 75, 2 to 50, 3 to 25, 4 to 0), so the higher score indicate better health-related quality of life. If greater than 50 percent of the items within a dimension are missing then the dimension score will not be computed, otherwise the mean score for the dimension will be calculated as the sum of items over the number of items answered.

A Psychosocial Health Summary Score will be calculated as the sum of items over the number of items answered in the emotional, social and school functioning dimensions. A Total Score will be calculated as the sum of all the items over the number of items answered on all dimensions. If greater than 50 percent of the items are missing, then the summary score or total score will be set to be missing.

The actual score as well as change from baseline score for Emotional, Social and School Functioning Scale Score, Physical Health Summary Score, Psychosocial Health Summary Score as well as Total Scale Score will be summarized by visit. Subject listings will also be provided. Figures may be presented in addition to subject listings and summary tables as appropriate.

4.2.4.4. Electrophysiology

Electrophysiology endpoints will include the Visual Evoked Potential (VEP), Brain Stem Auditory Evoked Response (BAER). VEP will be assessed at Screening, Month 12 and Month 24, while BAER will be assessed at Screening and Month 24. A Subjects listing will be provided.

4.2.4.5. Health Economic Data

Health economic data are collected at every scheduled visit from week 2 to Month 24, including number and reason for hospitalization and clinic visits and serviced received since last visit. Subject listings will be provided.

4.2.4.6. Socioeconomic Status (SES)

SES will be assessed by obtaining maternal and paternal occupations and years of education based on a formula developed by Hollingshead and Redlich (Hollingshead and Redlich 1954; Hollingshead and Redlich 2007). A subject listing will be provided.

4.2.4.7. Global Assessment

Global behavioral assessment scores are collected at pre-conditioning and follow up month 12 and 24. Parents/caregiver are asked to provide qualitative assessment on their child's behavior in the following 7 items: Arousal, Focus, Impulsivity, Motivation, Word Retrieval, Visual and Auditory processing. Each item is scored on a 4-point ordinal scale (1=No difficulty, 2=Some difficulty but able to participate in testing, 3=A lot of difficulty; can participate only with ample external support, 4=Caused inability to be tested).

A Global Assessment Total Score will be calculated as the sum of all the items over the number of items answered on all dimensions If greater than 50 percent of the items are missing, then the summary score or total score will be set to be missing.

The actual score in each dimension will be summarized categorically by visit, the number and percentage of subjects on each scheduled visit will be presented. The Total Score and its change from baseline value will be summarized by visit. A Subject listing will also be provided. Figures may be presented in addition to subject listings and summary tables as appropriate.

4.3. Safety Analyses

4.3.1. Overview of Safety Analyses

Statistical methods will generally consist of descriptive statistics and exact 2-sided 95% CI as appropriate. If a subject treated with eli-cel undergoes an allo-HSCT during study, additional analysis will be conducted with the study divided into an eli-cel and allo-HSCT period as outlined in Section 3.

Table 4 is a summary of the populations used for the safety analyses.

Table 4: Safety Analyses

Safety Endpoints/Parameters	Analysis Population
Neutrophil engraftment Platelet engraftment	TP
Proportion of subjects who experience either acute (≥ Grade II) or chronic GVHD by Month 24 Proportion of subjects with ≥ Grade II acute GVHD by Month 24 Proportion of subjects with chronic GVHD by Month 24	TP
Transplant-related mortality	TP
Proportion of subjects undergoing an allo-HSCT by Month 24	TP
AEs/SAEs	ITT
Laboratory parameters	ITT
Post-NE hospitalizations, ICU visits, ER visits	NEP

Number of subjects in whom vector derived replication competent lentivirus (RCL) is confirmed by Month 24	TP
The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.) by Month 24 The number of subjects with persistent oligoclonality by Month 24	TP
Concomitant medications/procedures	ITT
Vital signs	ITT

4.3.2. Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects with neutrophil engraftment after eli-cel infusion.

Neutrophil engraftment (NE) is defined as achieving 3 consecutive absolute neutrophil count (ANC) laboratory values of $\geq 0.5\times10^9$ cells/L (after initial post-infusion nadir) obtained on different days by 42 days post-infusion of eli-cel (Rel Day 43). The first day of the 3 different days with ANC $\geq 0.5\times10^9$ cells/L is considered the date of engraftment, with clinical confirmation if needed. If ANCs are not collected on a day but the white blood cell (WBC) count is less than 0.75×10^9 cells/L, the ANC is considered to be $< 0.5\times10^9$/L for the purposes of calculating day of neutrophil engraftment.

The proportion of subjects achieving NE by Rel Day 43 will be provided along with the 2-sided exact 95% CI. This analysis will be based on subjects who are evaluable for NE, which includes subjects who achieved NE by Rel Day 43, or had discontinued or were lost to follow-up before Rel Day 43 without achieving NE, or was followed to at least Rel Day 43 (Rel Day of DLC ≥ 43) but haven't achieved NE. Subjects who did not achieve NE by Rel Day 43, or who discontinued or were lost to follow-up before Rel Day 43 without achieving NE, are considered failures for NE.

4.3.3. Secondary Safety Endpoints

4.3.3.1. GVHD

The number and percent of subjects will be provided along with the exact 95% CI for the TP for the following safety endpoints separately:

- Proportion of subjects with ≥ Grade II acute GVHD or chronic GVHD by Month 24
- Proportion of subjects with ≥ Grade II acute GVHD by Month 24
- Proportion of subjects with chronic GVHD by Month 24

Evaluable subjects are defined as those who had GVHD by Month 24 (Rel Day 730), or have been followed for at least 12 months (Rel Day of DLC ≥ 365) without GVHD.

Subjects who had GVHD at any time during the study will be provided in a listing.

4.3.3.2. Transplant-Related Mortality

Transplant-related mortality is determined by the Investigator and summarized for the following intervals: from Rel Day 1 through 100 days post-eli-cel infusion (Rel Day 101) and from Rel Day 1 through 365 days post-Eli-cel infusion (Rel Day 366). The number and percent of transplant-related deaths as well as the exact 95% CIs will be presented for the TP. Evaluable subjects include those who have died from transplant-related causes by Rel Day 101 or 366 respectively or have been followed to at least Rel Day 101 or 366 respectively without transplant related mortality.

4.3.3.3. Loss of Engraftment

All analyses in this sub-section will be based on the TP unless otherwise specified.

Engraftment Failure

A subject is considered to have primary engraftment failure if he does not achieve NE by Rel Day 43. The number and proportion of subjects who have primary engraftment failure will be provided along with two-sided exact 95% CI, based on subjects who are evaluable for NE as defined in above Section 4.3.2. Subjects who discontinued or were lost to follow-up before Rel Day 43 without achieving NE are considered to have primary engraftment failure.

A subject is considered to have secondary engraftment failure if he achieves and then subsequently loses NE by Month 24, i.e., if the subject meets both of the following conditions:

- Achieved NE by Rel Day 43 as defined above;

- Has sustained decline in ANC to < 0.5×10^9 cells/L for 3 consecutive measurements on different days after Rel Day 43, without alternate etiology.

The first day of the 3 consecutive ANC decline to < 0.5×10^9 cells/L is the day of secondary engraftment failure.

The proportion of subjects who have secondary engraftment failure by Month 24 will also be provided along with 2-sided exact 95% CIs for the TP. This analysis will be based on subjects who are evaluable for secondary engraftment failure by Month 24, which includes subjects who have achieved NE, and satisfy any of the following conditions: 1) have secondary engraftment failure by Rel Day 730, 2) have been followed for at least 24 months (Rel Day of DLC ≥ 730 or completed Month 24 Visit) if no secondary engraftment failure.

The number and proportion of subjects who have primary or secondary engraftment failure by Month 24 (Rel Day 730) will be provided along with the 2-sided exact 95% CI. Evaluable subjects include subjects, who had either primary engraftment failure or secondary engraftment failure by Month 24 (Rel Day 730), or have been followed for at least 24 months (Rel Day of DLC ≥ 730 or completed Month 24 Visit) if no primary or secondary engraftment failure.

4.3.3.4. Time to Neutrophil Engraftment

The time to NE will be descriptively summarized for subjects who achieved NE. The definition of NE is defined in Section 4.3.2.

4.3.3.5. Platelet Engraftment

Platelet engraftment (PE) is defined as achieving 3 consecutive unsupported platelet counts of ≥ 20×10^9 cells/L (after initial post-infusion nadir) obtained on different days while no platelet transfusions are administered for 7 days immediately preceding and during the evaluation period, with clinical confirmation as needed.

The first day of 3 consecutive platelet counts ≥ 20×10^9 cells/L is the day of platelet engraftment.

The proportion of subjects who achieved platelet engraftment by Month 24 will be provided along with 2-sided 95% exact CI. This analysis will be based on subjects who are evaluable for PE by Month 24, which includes subjects who achieve PE by Month 24 (Rel Day 730), or have been followed for at least 24 months (Rel Day of DLC ≥ 730 or completed of Month 24 visit) if no platelet engraftment.

The time to PE will be descriptively summarized for subjects who achieved PE.

4.3.3.6. In-Patient Hospitalizations, ICU Stays, Emergency Room Visits

In-patient hospitalizations, ICU and emergency room visits are generally referred to as hospitalization in this section. Hospitalization with pre-NE admission is defined as hospitalization with admission date before the day of NE achievement; hospitalization with post-NE admission is defined as those with admission date on or after the day of NE achievement.

Subjects with inpatient transplant are defined as subjects who stay in hospital after infusion and achieve NE in hospital, and subjects with outpatient transplant are defined as subjects who are discharged from hospital after infusion and may achieve NE out of hospital.

The safety endpoints listed below will be summarized:

- Number and total duration of in-patient hospitalizations
- Number and total duration of ICU stays
- Number of emergency room visits

The summary will be done separately for hospitalization with pre-NE admission and post-NE admission. Hospitalization with pre-NE admission includes summary for inpatient transplant and outpatient transplant. Hospitalization with post-NE admission will be summarized for the following sub-periods:

- Post-NE to M6 (Rel Day 182)
- >M6 (Rel Day 183) to M12 (Rel Day 365)
- >M12 (Rel Day 366) to M24 (DLC in ALD-104)
- Post-NE to M12 (Rel Day 365)
- Post-NE to M24 (DLC in ALD-104)

The hospitalization will be counted in the sub-periods if admission time falls into that sub-periods. Overlapping hospitalizations within the same time window are combined as one hospitalization for summary.

4.3.3.7. Vector-derived replication competent lentivirus (RCL)

Blood samples for RCL testing will be collected and tested using a RCL screening assay as well as a confirmatory assay if the screening assay is positive. The RCL screening results will be summarized as well as co-culture results if RCL tested positive. Number and proportion of subjects with RCL detected by Month 24 will be tabulated if there is more than or equal to 1 case post infusion of eli-cel. Evaluable subjects include subjects with at least 1 RCL assessment post

infusion of eli-cel. A listing of all collected data from screening and confirmatory testing as well as those collected post eli-cel infusion will be provided.

4.3.3.8. Allo-HSCT

The proportion of subjects who undergo allo-HSCT by Month 24 will be provided along with exact 95% CI for the TP. The evaluable set includes subjects who decided to receive allo-HSCT or subjects who have been followed for at least 24 months (Rel Day of DLC ≥ 730 or completed Month 24 visit) without discontinuing to receive a subsequent allo-HSCT.

4.3.3.9. Insertional oncogenesis

The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.) post-drug product infusion by Month 24 will be provided in a listing. Events of malignancies will be reviewed via bluebird bio safety governance process to determine the root cause and if any event meets the insertional oncogenesis endpoint.

4.3.4. Exploratory Safety Endpoint

4.3.4.1. Integration Site Analysis (ISA) and Assessment of Oligoclonality

Integration site analysis (ISA) will be performed to determine the insertion site (IS) profile of subjects over time per SOE in Protocol.

Figure 1 shows the algorithm that determines the frequency of monitoring by ISA to assess oligoclonality, in accordance with FDA Guidance (FDA 2020) and based on FDA consultation. While oligoclonality itself, or even monoclonality, will not a priori result in a malignancy, changes in IS relative frequency may be associated with an increase in the risk of a malignancy. Therefore, ISA monitoring is performed every 3 months from Month 6 to Month 12, every 4 months start from Month 16 to Month 24 throughout the study. This is coupled with monitoring for hematological abnormalities via CBC with differential every month from Month 1 to Month 12, every 4 month start from Month 16 to Month 24 throughout the study.

ISA monitoring may be repeated more frequently if there is an indication of oligoclonality or if ISA should otherwise be triggered (see protocol Section 6.5.11.1.2 for more details on triggered BM evaluations). Such triggers include (but are not limited to) persistent unexpected CBC abnormalities (including persistent [i.e., two consecutive] CTCAE Grade 2 CBC values), post-discharge blood transfusion (unless due to trauma or a procedure/intervention), or a two-fold increase in peripheral blood vector copy number (PB VCN) over a 4 or 6-month period (based on

the SOE in Protocol), or other abnormal results from a subject's most recent BM biopsy or aspirate or ISA findings of potential oligoclonality or IS in a known oncogene.

If an IS is detected at ≥ 10% RelFreq or an IS ≥ 5% RelFreq is detected in 2 or more IS, this would be considered "*oligoclonality*" and ISA will be repeated within 3 months of receipt of this result. If an IS ≥ 10% or 2 or more IS ≥ 5% are confirmed, then a report of "*persistent oligoclonality*" will be submitted by the Sponsor to the relevant Health Authorities within 30 days of receipt of the ISA report confirming an IS meeting the criteria for persistent oligoclonality. This repeated observation will also trigger enhanced monitoring for hematological abnormalities, increasing the frequency of CBC with differential to every 3 months (if not already occurring at the interval) until the frequency no longer meets oligoclonality criteria. Persistent oligoclonality also triggers BM assessment (for the frequency of subsequent BM assessments (see protocol Section 6.5.11.1.2). If persistent oligoclonality is not observed after initial repeat testing, CBC and other monitoring reverts to routine assessments per the SOE in Protocol.

Additionally, if an IS is detected at ≥ 5% RelFreq in a known oncogene (based upon Tier 1 oncogenes in the CGC in the COSMIC at the time of the ISA report review), then ISA (and VCN) will be repeated within 3 months of receipt of this result. If an IS in a known oncogene is confirmed during re-evaluation it would be considered persistent. This repeated observation will trigger enhanced monitoring for hematological abnormalities, including a BM evaluation and increasing the frequency of CBC with differential to every 3 months (if not already occurring at the interval) until the frequency no longer meets criteria. ISA and VCN will continued per the SOE in Protocol.

Top 10 IS data will be analyzed to identify IS that are repeated at consecutive visits within a subject and also IS-associated genes that are repeated in multiple subjects.

The total number of unique mappable IS in PBLs at each visit, as well as the highest frequency and highest total number of unique mappable IS within subject across all visits, will be summarized. Additional analysis may be performed as appropriate.

Subject listing will be provided for all integration site analysis results.

Persistent oligoclonality at any time is defined as an IS ≥ 10% RelFreq in an initial ISA, and the IS ≥ 10% RelFreq results are confirmed in the subsequent ISA; or at least 2 IS ≥ 5% RelFreq in an initial ISA, and the same IS ≥ 5% RelFreq results are confirmed in the subsequent ISA.

Current persistent oligoclonality is defined as an IS ≥10% RelFreq in an initial ISA, the IS ≥ 10% RelFreq results are confirmed in the subsequent ISA, and the ≥ 10% RelFreq is maintained through the last two ISA as of the data cut-off date; or at least 2 IS ≥ 5% RelFreq in an initial ISA, the same IS ≥ 5% RelFreq results are confirmed in the subsequent ISA, and the ≥ 5% RelFreq is maintained through the last two ISA as of the data cut-off date.

Current oligoclonality is defined as an IS ≥ 10% RelFreq the first time at most recent ISA as of the data cut-off date; or at least 2 IS ≥ 5% RelFreq the first time at most recent ISA as of the data cut-off date.

The number and percentage of subjects who meet the persistent oligoclonality at any time, current persistent oligoclonality, current oligoclonality criteria will be summarized. A subject listing of oligoclonality criteria will be provided.

Details on persistent oligoclonality assessment are presented as a schematic in Figure 1.

The number and percentage of subjects who meet the persistent oligoclonality, current persistent oligoclonality, and current oligoclonality criteria by Month 24 will be summarized. Additionally, subjects meeting oligoclonality criteria will be identified, along with the pertinent IS.

IS RelFreq overtime will be plotted for subjects with IS meeting the current persistent oligoclonality and current oligoclonality criteria.

Top 10 RelFreq results for each subject overtime will be presented in listings.

In addition, the total number of unique mappable IS in PBLs at each visit, as well as the highest frequency and highest total number of unique mappable IS within subjects across all visits, will be summarized. Additional analysis may be performed as appropriate.

Persistent IS in known oncogene is defined as defined as RelFreq of ⩾ 5% for the same IS in known oncogene at two consecutive timepoints. Known oncogene is defined as a gene classified as Tier 1 in the Cancer Gene Census (CGC) in the Catalogue of Somatic Mutations in Cancer (COSMIC) at the time of the ISA report review.

Persistent IS in known oncogene at any time is defined as a subject meeting the criteria of persistent IS in known oncogene at any time during the study, including cases when the criteria are no longer met in later follow-up assessments.

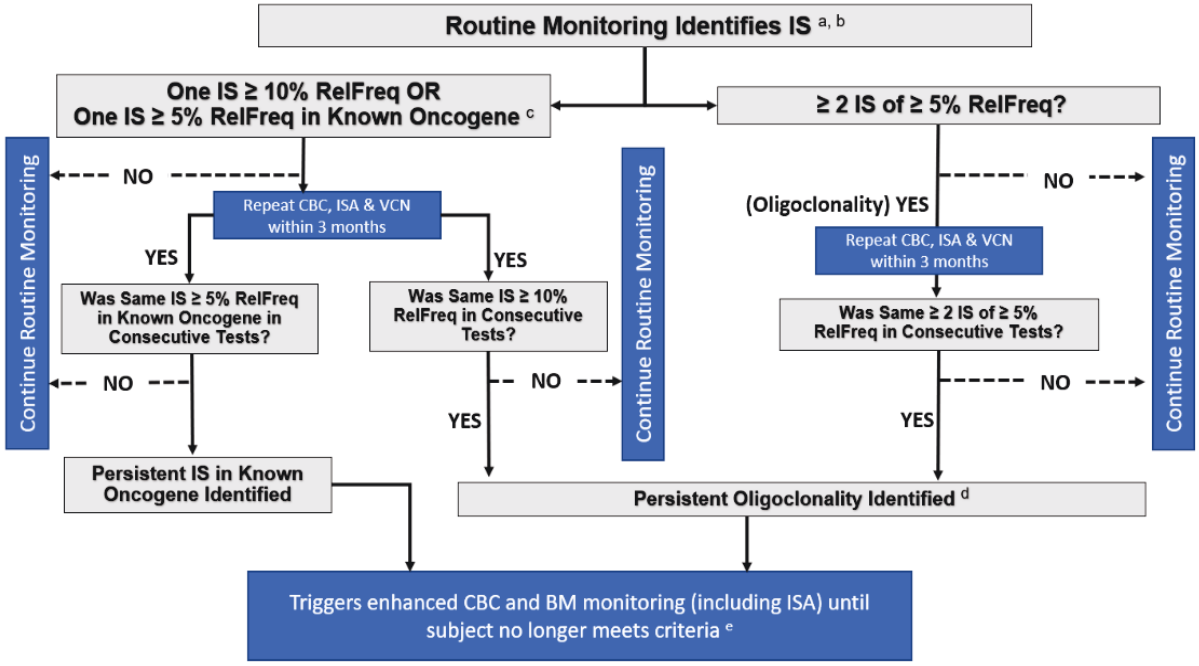
Current persistent IS in known oncogene is defined as a subject meeting the criteria of persistent IS in known oncogene at the last two assessments as of the data cut-off. It is a subset of persistent IS in known oncogene at any time.

Current IS in known oncogene is defined as at least 1 IS ⩾5% RelFreq in known oncogene at the last assessment as of the data cut-off.

The number and percentage of subjects meeting persistent IS in known oncogene at any time, current persistent IS in known oncogene, and current IS in known oncogene will also be summarized.

A sensitivity analysis will be performed to only include the assessments for subjects within the eli-cel period.

Figure 1: ISA Triggered Enhanced Monitoring



Abbrev.: BM, bone marrow; CBC, complete blood count with differential; IS, insertion site(s); ISA, integration site analysis; RelFreq, relative frequency; VCN, vector copy number.

a ISA, VCN, CBC schedule is specified in protocol Section 6.1.

b IS can be measured from different types of samples (peripheral blood or bone marrow). If an IS is found at a higher frequency in a bone marrow sample (e.g., triggered by persistent ISA findings) than in a peripheral blood sample, then that bone marrow frequency would be used to assess followup.

c Tier 1 oncogenes in the Cancer Gene Census (CGC) of the Catalogue of Somatic Mutations in Cancer (COSMIC) at the time of the ISA report review.

d "Persistent oligoclonality" will be reported (once per pertinent IS/set of IS) to applicable Health Authorities within 30 days of receipt of applicable repeat ISA result.

e Observation of Persistent Oligoclonality triggers increasing the frequency of CBC with differential and bone marrow assessment to every 3 months (if not already occurring at the interval) along with ISA and VCN every 6 months until the frequency no longer meets criteria.

4.3.5. Adverse Events (AE)

Overall summary of AE distribution will be tabulated.

All AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for each of the Study Periods defined in Section 3.6. Subjects at risk for each period is defined to be the subjects who enter the period.

Treatment emergent AEs (TEAE) are defined as AEs occurring at or after the initiation of eli-cel infusion. TEAEs will be summarized for the Study Periods D1 to M12, >M12 to M24, D1 to M24 as defined in Section 3.6.

Summary of AEs by SOC and PT for each Study Period will be tabulated for the following:

- All AEs
- All SAEs
- All non-serious AEs
- Grade 3 or higher AEs
- Grade 3 or higher AEs of infections
- Grade 3 or higher AEs related to eli-cel
- Grade 4 or higher AEs
- All eli-cel related AEs
- All eli-cel related SAEs
- AEs attributed to mobilization/apheresis
- AEs attributed to conditioning
- AEs attributed to study procedure
- AEs attributed to disease under study or disease progression
- Treatment-emergent Events of Interest (EOI):
    - HIV infection: MedDRA HLT = Acquired immunodeficiency syndromes, Retroviral infections
    - Autoimmune Disease/Immunogenicity/long latency hypersensitivity:
        - MedDRA HLGT = Autoimmune disorders
        - MedDRA HLT = Autoimmunity analyses, Anaemias hemolytic immune
        - MedDRA PTs = Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Acute graft versus host disease oral, Chronic graft versus host

disease, Chronic graft versus host disease in intestine, Chronic graft versus host disease in liver, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in lung, Graft versus host disease in skin, Transfusion associated graft versus host disease, Chronic graft versus host disease in eye, Chronic graft versus host disease oral

  - Infections: MedDRA SOC = Infections and Infestations
  - Bleeding events: MedDRA SMQ= Haemorrhages
  - Malignancies: MedDRA SMQ = Malignant tumors, Malignant lymphomas, Myelodysplastic syndrome, Blood premalignant disorders
- AEs leading to early termination
- AEs leading to death

Summary of AEs by SOC or PT and number of events within each period might be presented when appropriate.

Listing will be provided for AEs, SAEs, eli-cel related AEs, AEs attributed to mobilization/apheresis, AEs attributed to conditioning, AEs attributed to study procedure, AEs attributed to disease under study or disease progression, EOI subcategories, AEs leading to early termination and death. Study period will be included in the listing.

4.3.6. Laboratory Analysis

Clinical laboratory values will be expressed using the International System of Units (SI).

Internationally accepted reference ranges for children as published by the Mayo Clinic, the New England Journal of Medicine (NEJM) and the Journal of Allergy and Clinical Immunology (for the immunological ranges) will be utilized. For purposes of this analysis plan, these ranges are referred to as Global Reference Ranges (GRRs). Age-specific and gender specific ranges will be used to flag out-of-range values and to categorize into CTCAE (version 4.03) grades where applicable.

Hematology, Clinical Chemistry, Liver and Adrenal Function

The following clinical laboratory parameters are collected during the study:

Hematology: CBC with differential	
Hematocrit	White blood cell (WBC) count with differential
Hemoglobin	Platelet count

Red blood cell (RBC) count	Peripheral blood smear
Clinical chemistry	
Sodium (Na)	Blood urea nitrogen (BUN)
Potassium (K)	Creatinine
Chloride (Cl)	Glucose
Magnesium (Mg)	Calcium (Ca)
Phosphorus (P)	
Liver Function Tests	
Aspartate aminotransferase (AST)	Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)	Bilirubin (total and direct)
Adrenal Function Tests	
Cortisol	Adrenocorticotropic hormone (ACTH)
Aldosterone	Plasma renin activity

Descriptive statistics will be tabulated for the value and change from Baseline for the collected clinical laboratory parameters by visit. Box plots for neutrophil and platelet may be presented.

Change from Baseline will be included in subject level data listings.

Number and percentage of subjects with ≥ Grade 3 prolonged cytopenia (i.e., decreased platelet counts, decreased neutrophil counts, and/or decreased hemoglobin counts) on or after Rel Day 60 and Rel Day 100 will be tabulated. A listings of laboratory values for subjects with ≥ Grade 3 prolonged cytopenia on or after Rel Day 60 will also be provided.

Potentially clinically significant (PCS) laboratory values in this study are defined as follows:

Laboratory Test	PCS Threshold
Hematology	
Leukocytes	<4.0 x 10^9/L or ≥18 x 10^9/L

Neutrophils	<1.0 x 10^9/L
Erythrocytes	≤3.0 x 10^12/L
Hemoglobin	≤8.0 g/dL
Platelets	≤75 x 10^9/L
Liver	
Alanine Aminotransferase	≥3 x ULN
Aspartate Aminotransferase	≥3 x ULN
Alkaline Phosphatase	≥3 x ULN
Bilirubin	≥34.2 umol/L
Renal	
Urea Nitrogen	≥10.7 mmol/L
Creatinine	≥150 umol/L
Electrolytes	
Sodium	≤126 mmol/L or ≥156 mmol/L
Potassium	≤3 mmol/L or ≥6 mmol/L
Other	
Glucose	≤3.0 mmol/L

The number and proportion of subjects with PCS laboratory values will be presented for the study periods as defined in Section 3.6.

Immunological Studies

The value and change from Baseline for the following immunological parameters will be presented in subject level listings:

- T cell subsets: CD4, CD8

- B cells: CD19
- NK cells: CD16 or CD56
- Immunoglobulins: IgG, IgM, IgA

In addition, serology and additional lab tests will be listed separately.

4.3.7. Vital Signs and Physical Examinations

4.3.7.1. Vital Signs

Vital sign data to be presented includes weight, height, BMI, systolic and diastolic blood pressures, heart rate, respiration rate, and temperature.

The value and change from Baseline for vital signs will be summarized at protocol-specified assessment time points.

The subject level listing for vital signs will include the value and change from Baseline.

4.3.7.2. Physical/Neurological Examination Results

The neurological examination is conducted for the following areas: visual acuity and vision field defects, hearing/auditory processing problems, speech, swallowing function, motor function, muscle tone, sensory examination (upper extremities, lower extremities), Babinski or Plantar reflex, deep tendon reflexes, and coordination/cerebellar function. The status (normal/abnormal) for each area will be presented in a subject level listing.

Physical examination status will be reported by system as 'normal', 'abnormal not clinically significant', or 'abnormal clinically significant' at Baseline and at each post-baseline assessment as noted in the SOE of the protocol. All physical examination findings will be presented in a subject level listing.

4.3.8. Echo- and electro-cardiograms

Echo- and electro-cardiogram data will be provided in a subject-level listing.

4.3.9. Concomitant Medications and Procedures

Medications will be coded using the WHO Drug Dictionary, the version of WHO Drug Dictionary will be determined at the time of analysis.

Medications will be assigned to one or more study periods of the following study periods as defined in Section 3.6, based on the medication start and end dates relative to the study periods.

Concomitant medications will be summarized by the anatomic therapeutic class (ATC) and preferred term for each of the above study periods. G-CSF usage will also be summarized for each of study periods as defined in Section 3.6.

The assigned study periods will be included in the subject level listing on medications/procedures.

Concomitant treatments/procedures will be displayed in a separate listing.

5. CHANGES TO PLANNED ANALYSES

5.1. Changes from Study Protocol

None

5.2. Changes from Previous SAP

Version	Date	Change from the Previous Version
1.0	30 October 2019	Initial version
2.0	16 November 2020	N/A
3.0	29 March 2021	N/A
4.0	5 Oct 2022	1. Updated the responsible Medical Officer and the approvers. 2. Throughout change "at Month 24" to "by Month 24" for secondary safety endpoint of GVHD 3. Section 3.12, clarified that delayed visit summary on COVID impact will only include post infusion visits 4. Section 4.3.4, specify ISA will be performed as protocol specified 5. Section 3.2, specify added additional analysis will be conducted for subject who undergoes allo-hsct 6. Section 4.3.3, add subsection 4.3.3.4 to line up with protocol, since it's an secondary endpoint. 7. Section 4.1.2, add 1 item
		8. Add section 1.2.4, DMC 9. Section 4.3.5, add Grade 3 or higher AEs of infections 10. Section 3.5, Analysis time windows revised per SOE in protocol 11. Section 4.3.5, per PV, added MedDRA PT = Acute graft versus host disease oral, Chronic graft versus host disease in eye, Chronic graft versus host disease oral

Version	Date	Change from the Previous Version
	08 Aug 2023	12. Section 3.5, ISA visit window updated, hematology visit window added week 2 13. Section 4.3.4.1, A sensitivity analysis will be performed to only include the assessments for subjects within the eli-cel period. 14. Section 3.2, For subjects who don't have allo, Eli-cel period begins from day of eli-cel infusion (Rel Day 1) up to the DLC.

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