STATISTICAL ANALYSIS PLAN

A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced with Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD)

Protocol ALD-102

Protocol Number:	ALD-102
Protocol Version and Date:	Version 10.0: 23 September 2020
Name of Test Drug:	elivaldogene autotemcel (also known as Lenti-D Drug Product)
Phase:	Phase 2/3
Methodology:	Single arm, multi-site, single dose study
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Analysis Plan Date:	22 March 2021
Analysis Plan Version:	4.0

[redacted]

APPROVAL OF THE STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

Title: A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced with Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD)

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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
CCI	PPI [redacted]
CALD	Cerebral adrenoleukodystrophy
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLC	Day of last contact
EOI	Events of interest
EOS	End of study
CCI	CCI [redacted]
GdE	Gadolinium enhancement
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigens, encoded by the human major histocompatibility locus
HLT	High-Level Term
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
ITT	Intent-to-treat
IS	Integration site
ISA	Integration site analysis
IV	Intravenous
LLN	Lower limit of normal
LVV	Lentiviral vector
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Major functional disability
MRI	Magnetic resonance imaging
MMP	Matrix metalloproteinase
NE	Neutrophil engraftment

Abbreviation	Definition
NEP	Successful neutrophil engraftment population
NFS	Neurologic Function Score
PB	Peripheral blood
PBLs	Peripheral blood leukocytes
PCS	Potentially Clinically Significant
CCI	CCI
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	Standardised MedDRA Queries
SOE	Schedule of Events
SOC	System Organ Class
TP	Transplant population
TRNE	Transplantation to neutrophil engraftment
TxI	Transduction Index
ULN	Upper limit of normal
US	United States
CCI	CCI
VCN	Vector copy number
VLCFA	Very long chain fatty acids

[redacted]

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 ALD-102, which are to evaluate the efficacy and safety of elivaldogene autotemcel (also known as Lenti-D Drug Product and hereafter referred to as eli-cel) in subjects with cerebral adrenoleukodystrophy (CALD). This SAP is based upon Protocol ALD-102 v10.0, dated 23 September 2020.

The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the ALD-102 clinical study report (CSR). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described.

A separate inter-study SAP describes comparisons of data from this study and its long-term extension Study LTF-304 with data from a retrospective data collection study of CALD (Study ALD-101) and a contemporaneous external control study of allogeneic hematopoietic stem cell transplantation (allo-HSCT)-treated patients with CALD (Study ALD-103).

1.2. Synopsis of Study Design

Study ALD-102 is an international, single-arm, multi-site, single-dose study in males ≤17 years of age with CALD who do not have a willing 10/10 HLA matched sibling donor. The study objectives are to evaluate the efficacy and safety of a single intravenous (IV) administration of eli-cel in subjects with CALD.

The study was initially designed to enroll up to 15 subjects in order to obtain at least 12 evaluable subjects. As of October 2015, under Protocol versions 2.0-6.2, there were 17 subjects enrolled and treated with eli-cel as well as 1 screen failure. Analysis of these 17 subjects will be the basis for determining the success or failure of the study.

In order to obtain experience with the European contract manufacturing organization and to continue to provide a treatment option for patients who could benefit from eli-cel in a controlled setting, the Study Protocol was later amended to treat approximately 30 subjects. Despite the addition of this second cohort of subjects, the nature of the primary analysis (based on the cohort of the first 17 treated subjects) has not changed. A final analysis including all treated subjects will also be performed when all subjects complete the study.

Study endpoints are described in Section 2.2 of the Study ALD-102 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
- 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 G- CSF-mediated, and potentially plerixafor-mediated, hematopoietic stem cell (HSC) mobilization and harvest by apheresis using institutional practice treatment guidelines. G-CSF is defined in the study 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, stored frozen in cryopreservative 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 undergoes conditioning with cyclophosphamide IV and busulfan IV.

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 Study ALD-102 Protocol. Then, if appropriate consent (or assent, if applicable) is obtained, subjects will be followed for an additional 13 years under a separate follow-up protocol (Study LTF-304).

1.3. Efficacy, Safety, and Exploratory Endpoints

The efficacy, safety, and exploratory endpoints are listed below from the study Protocol Section 2.2. Detailed definitions and analysis methods of the endpoints are provided in Section 4.

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 who demonstrate resolution of gadolinium positivity on magnetic resonance imaging (MRI) (i.e., GdE-) at Month 24
- Time to sustained resolution of gadolinium positivity on MRI (i.e., GdE-). Sustained is defined as gadolinium resolution without a subsequent evaluation indicating gadolinium positivity
- Change in total Neurologic Function Score (NFS) from Baseline to Month 24
- MFD-free survival over time
- Overall survival

Exploratory efficacy endpoints are the following at Month 24:

CCI [redacted]

1.3.2. Safety Endpoints

The primary safety endpoint is:

- The proportion of subjects who experience either acute (≥ Grade II) or chronic graft- versus-host disease (GVHD) by Month 24

The secondary safety endpoints are:

- Proportion of subjects with neutrophil engraftment (NE) by 42 days post-infusion of eli-cel
- Time to neutrophil engraftment post-infusion of eli-cel
- Proportion of subjects with platelet engraftment by Month 24
- Time to platelet engraftment post-infusion of eli-cel
- Proportion of subjects with loss of engraftment post-infusion of eli-cel by Month 24
- Proportion of subjects who undergo a subsequent HSC infusion by Month 24

- Proportion of subjects with transplant-related mortality through 100 and 365 days post-infusion of eli-cel
- Proportion of subjects with and severity of clinical ≥ Grade 3 AEs, all drug-product related AEs, all serious adverse events (SAEs), ≥ Grade 3 infections, and changes in laboratory parameters by Month 24
- Proportion of subjects with ≥ Grade II acute GVHD by Month 24
- Proportion of subjects with 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
- Incidence of vector-derived replication competent lentivirus (RCL) by Month 24
- The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.) by Month 24

The exploratory safety endpoint is:

- CCI [redacted]

CCI [redacted]

1.3.3. Other Exploratory Endpoints

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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 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. Subject Cohorts

Tabulations and figures will be produced for appropriate demographic, baseline, efficacy, safety, and exploratory parameters for one or all of the groups below:

- Initial Study Cohort: includes the first 18 subjects screened in Study ALD-102 (under Protocol versions 2.0-6.2). Within this cohort, 1 subject failed screening and did not receive any study treatment, while 17 subjects enrolled in the study and were treated with eli-cel.
- Overall Study Cohort: includes all screened subjects. This cohort includes the Initial Study Cohort as well as the additional subjects who were screened afterwards.

The combination of cohorts and analysis populations (defined in Section 2.1) specify the subjects to be included in an analysis.

2.3. 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 30. The sample size for this study was not determined by formal statistical methods. The rarity, severity, and rapidly progressive nature of CALD significantly constrain enrollment. For example, from 2009 through 2013, there were approximately 20 to 24 allo-HSCTs per year performed on subjects with CALD in the US (http://www.cibmtr.org).

3.1.1. Success Criterion

The success criterion for this study is based on a comparison of the Study ALD-102 primary efficacy endpoint for the Initial Study Cohort to a clinically meaningful benchmark, such that the lower bound of the 2-sided 95% exact CI of Month-24 MFD-free survival must be >50% in order for the primary endpoint to be met. This success criterion would be met with a point estimate of 76.5% (13 of 17 subjects) in the Initial Study Cohort.

This clinically meaningful benchmark of 50% is supported by the Study ALD-101 untreated study population, who were GdE+ at any time, as well as data from the Study ALD-101 allo- HSCT treated population, now published in the literature (Raymond et al., 2018). There is additional supportive context from disease-specific literature that reports on overall survival rather than MFD-free survival (Baumann et al., 2003; Beam et al., 2007; Miller et al., 2011; Peters et al., 2004). Because patients can and do progress through MFDs to death, the results of these studies can be further informative to this benchmark.

In Study ALD-101, the Month-24 MFD-free survival rate in untreated GdE+ subjects within 2 years of their first GdE+ MRI was 21% (exact 95% CI: 6.1% to 45.6%). Thus, this benchmark value is above the upper bound of the 95% CI of the Month-24 MFD-free survival in untreated subjects in Study ALD-101.

In Study ALD-101, the lower bound of the 2-sided 95% exact CI of the Month-24 MFD-free survival rate in GdE+, early disease (NFS≤1, Loes ≥0.5 and ≤9) subjects without a matched sibling donor and treated with allo-HSCT was 50.1% (mean 76% with exact 95% CI of 50.1% to 93.2%).

An MFD-free survival rate at various timepoints ranging between approximately 50% to 90% is reported in existing literature for patients with CALD treated with allo-HSCT. Peters et al. reported that 53.4% of subjects treated with early clinical disease had no neurological progression and remained functional; the 5-year survival for subjects with 0 to 1 clinical symptoms at baseline was 67% to 70% (Peters et al., 2004). Miller et al. reported a 5- year survival rate of 91% (95% CI 69% to 98%) for patients with a baseline NFS of 0, and 89% (95% CI 70% to 96%) for patients with a baseline Loes score <10. The follow-up median NFS for both cohorts was 0, with an interquartile range of 0 to 0 (NFS of 0) and 0 to 1 (Loes score <10) (Miller et al., 2011). Both of these studies included subjects with matched sibling donors; however, subjects with a willing 10/10 HLA-matched sibling donor are excluded from Study ALD-102.

Similar rates are reported in two smaller studies: Beam et al and Bauman et al. Beam et al. reported an overall survival of 73% after approximately 4 years of follow-up post-allo- HSCT. Of the 6 patients who had baseline Loes scores ≤9, 5 (83%) patients were alive and functional (Beam et al., 2007). Baumann et al. reported 42% functional survival after approximately 3.7 years of follow-up. Of the 7 patients who had baseline Loes scores of ≤9 and GdE+, 6 (85.7%) patients were alive and functional (Baumann et al., 2003). The subjects in these studies had similarities to the Study ALD-102 population: both Beam et al. and Baumann et al. reported on subjects with baseline Loes scores ≤9 and the subjects in the Baumann comparison were gadolinium positive at baseline. Thus, a mean MFD-free survival rate greater than 70% would be consistent with the statistics reported in the literature.

3.2. General Methods

Statistical methods will be primarily descriptive in nature, and will include point estimates and confidence intervals (Cis) 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% 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 detailed in Section 4.2.3.1.

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

All outputs 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 19.0 or above. It is noted that coding of AEs may need to be updated based on the time of an analysis.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Version March 2016, or newer based 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. It should be noted Study Day 0 is used as the day of eli-cel infusion in Study ALD-102 Protocol Section 6.1, which is mainly for administrative use at investigation sites). Relative Month (Rel Month) may also be displayed where appropriate and will be calculated as Rel Month=Rel Day/30.4375.

For efficacy endpoints [redacted] baseline is defined as the non-missing assessment closest but prior to conditioning.

For safety endpoints, all laboratory data (including MMP and chitotriosidase levels), 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 or additional visit that is inside a visit window as defined in Table 1 below, the data from the unscheduled or additional visit will be used for the visit in data summaries. For subjects with multiple unscheduled or additional 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.

[redacted]

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 15**	**Month 18**	**Month 21**	**Month 24**
Target Rel Day (D)	D16	D31	D61	D91	D181	D271	D361	D451	D541	D631	D721
	Visit Window: First Day - Last Day										
Hematology Clinical chemistry	D2-23	D24-45	D46-75	D76-135	D136-225	D226-315	D316-405	D406-495	D496-585	D586-675	D676-DLC
ALDP, VCN		D2-45	D46-75	D76-135	D136-225	D226-315	D316-405	D406-495	D496-585	D586-675	D676-DLC
VLCFA				D2-135*	D2-270		D271-450		D451-630		D631-DLC
[redacted]											
MRI		D2-105			D106-270		D271-450		D451-630		D631-DLC

Note: DLC = Day of Last Contact.
*Visit window applies to subjects who enrolled under earlier versions of the Protocol (versions 2.0 to 4.0) and had VLCFA analyzed at Month 3. For these subjects their Month 6 VLCFA window will be D136-270.

3.6. Study Periods

For each subject, the study will be divided into the following Study Periods:

- ICF to < M: day of signed informed consent form (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, the end of this Study Period is DLC or End of Study [EOS] if the subject discontinues from the study without NE)
- NE to M12: day of NE to Rel Day 365 in Study ALD-102 (subjects who do not achieve NE will not be included in this study period)
- > M12 to M24: Rel Day 366 to DLC in Study ALD-102 (subjects who do not achieve NE will not be included in this study period)

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 stops 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.

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

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 periods.

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

- 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: day 1 (date/time of eli-cel infusion) to DLC in Study ALD- 102
- NE to M24: day of NE to DLC in Study ALD-102 (subjects who do not achieve NE will not be included in this study period)
- ICF to M24: day of signed ICF to DLC in Study ALD-102

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

- ICF to M24: day of signed ICF to DLC in Study-ALD-102

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 date 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.
  - The above exception does not apply to concomitant medications.
- If month and day 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.
  - The above exception does not apply to concomitant medications.
- 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 AE and concomitant medication end dates: if the day 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 1st of the month; if the day and month are both missing, the birth date will be set to Jan 1st.

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

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

The primary efficacy endpoint, Month-24 MFD-free survival, will be measured by comparing the rate to a clinically meaningful benchmark: the lower bound of the 2-sided 95% exact CI of the Month-24 MFD-free survival rate must be >50% (see Section 3.1.1 for rationale of benchmark).

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:

- Initial Analysis: to be performed after the Initial Study Cohort (enrolled under Protocol versions 2.0-6.2) complete the study or when the sponsor deems appropriate. This analysis will include all data from Initial Study Cohort and the Overall Study Cohort.
- Final Analysis: to 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, preparing for regulatory meetings,

and updating the scientific community. All analyses will utilize the same analysis methods and uniform success criterion 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 have study assessments performed at a health care 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 numbers and percentages of missed, delayed, and 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 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, the same approaches for treating missing data and imputations as laid out in Section 3.7 apply, i.e., the primary analyses will be based on available observed data, and use the same methods as specified in Section 4.2 and 4.3.

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

- For continuous variable endpoints, full-information maximum likelihood method may be used to estimate mean and variance at Month 24 and other time points, based on available longitudinal observations, SAS PROC CALIS will be used to carry out the analyses.
- For the proportion based endpoints, LOCF approach will be used.

[redacted]

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 2 is a summary of the subject cohorts and analysis populations to be used in the Initial Analysis and Final Analysis. Note that analyses based on the ITT population and NEP will only be performed if they are different from the TP.

Table 2: Analyses of Study Information

	Initial Study Cohort	Overall Study Cohort
Subject disposition	ITT	ITT
Analysis Populations	ITT	ITT
Demographics and baseline disease characteristics	ITT TP NEP	ITT TP NEP
Mobilization and apheresis	ITT	ITT
Conditioning	TP	TP
Eli-cel infusion	TP NEP	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 Study ALD-102 ITT population will be presented overall and by investigational site, for the following:

- Number and percentage of subjects who initiated mobilization
- Number and percentage of subjects who initiated conditioning
- Number and percentage of subjects who were infused with eli-cel
- Number and percentage of subjects who discontinued study, and reason for discontinuation
- Number and percentage of subjects who completed study, and subjects who enrolled in the long-term follow-up Study LTF-304
- Number and percentage of subjects who are in study at 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 of all subjects' duration of follow-up.

Additionally, the numbers and percentages of subjects in the TP who completed each follow-up study visits (Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24) will be tabulated. A tabulation of enrollment by site number and site country will also be presented.

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

4.1.3. Analysis Populations

The number and percentage 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
- Family history
- NFS at Baseline
- Loes score and Loes pattern at Baseline
- 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)
- Total dose of cyclophosphamide per kilogram (mg/kg)
- Estimated average daily AUC (µM*min/L) for busulfan.

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 his 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:

- Subject body weight at infusion (kg)
- VCN of eli-cel (eli-cel VCN; c/dg)
- Eli-cel total cell dose (CD34+ cells ×10^6/kg)
- Number and percentage of subjects that received rescue cells
- Percent lentiviral vector positive (% lentiviral vector [LVV]+) cells in eli-cel (eli- cel %LVV+ Cells)
- Vector copies per transduced cell (eli-cel VCN divided by eli-cel %LVV+ Cells)

Note: If a subject had multiple lots of eli-cel, the weighted average of eli-cel VCN, eli-cel %LVV+ Cells, and ratio of eli-cel VCN/eli-cel % LVV+ Cells using the fractions of cell dose (dose per lot/total dose of all lots) as the weight will be derived per subject (see Appendix, example for 2 lots).

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.

Table 3 is a summary of the study cohort and analysis populations used for efficacy in the Initial Analysis and Final Analysis. Note that analyses based on the ITT and NEP will only be performed if they are different from the TP.

Table 3: Analyses of Efficacy Endpoints

Efficacy Endpoints	Initial Study Cohort	Overall Study Cohort
Proportion of subjects who are alive and MFD-free at Month 24	ITT TP NEP	ITT TP NEP
MFD-free survival over time		TP
Overall survival		TP
Proportion of subjects who demonstrate resolution of gadolinium positivity at Month 24	TP	TP
Time to sustained resolution of gadolinium positivity on MRI		TP
Change in total NFS from Baseline to Month 24	TP	TP
Change in Loes score from Baseline to Month 24	TP	TP
Proportion of subjects who maintain an NFS ≤4 without an increase of >3 points from Baseline at Month 24	TP	TP
Proportion of subjects who maintain a Loes score ≤9 or not increasing a Loes score by ≥6 points from Baseline at Month 24	TP	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 percentage of subjects who achieve Month-24 MFD-free survival will be presented with the exact 95% CI for the TP. Failures for 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 the Initial Study Cohort and the Overall Study Cohort on Month 24 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 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 (See also Section 2.2).

Additionally, the number and percentage 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 and Exploratory Efficacy Endpoints

Analyses of all secondary CCI [redacted] 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 percentage 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 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 they will be censored at the DLC.
- Overall survival: For subjects who are alive, they will be censored at the DLC.

Deaths will be presented in by-subject listings.

4.2.3.2. 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 percentage of subjects who are GdE- at Month 24 will be provided with the exact 95% CI. The number and percentage 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 endpoints GdE- at Month 24 and sustained GdE- at Month 24 above, evaluable subjects are defined as subjects who have completed the Month 24 assessment.

4.2.3.3. Neurologic Function Score (NFS) and Loes Score

All MRIs will be assessed by a central reader(s) blinded to the subject identification, using the 34-point Loes scoring scale, which is widely used to diagnose and follow subjects with CALD. Loes pattern 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 and Loes Scores, 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 points 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 plotted by subject. Box plots of Loes score may also be provided.

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. The Overall Study Cohort will be presented for all safety analyses. Table 4 is a summary of the subject cohort and analysis populations used for safety in the Initial Analysis and Final Analysis.

Table 4: Safety Analyses

Safety Endpoints/Parameters	Initial Study Cohort	Overall Study Cohort
Proportion of subjects who experience either acute (≥ Grade II) or chronic GVHD by Month 24	TP	TP
Proportion of subjects with ≥ Grade II acute GVHD by Month 24	TP	TP
Proportion of subjects with chronic GVHD by Month 24	TP	TP
Transplant-related mortality	TP	TP
Engraftment and loss of neutrophil engraftment	TP	TP
Platelet engraftment	TP	TP
Proportion of subjects undergoing a subsequent allo-HSCT by Month 24	TP	TP
AEs/SAEs		ITT
Laboratory parameters		ITT
Post-NE hospitalizations, ICU stays, emergency room visits		NEP
Incidence of vector derived RCL by Month 24		TP
The number of subjects with insertional oncogenesis (myelodysplasia, leukemia, lymphoma, etc.) by Month 24		TP
The number of subjects with clonal predominance 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 who experience either acute GVHD (≥ Grade II) or chronic GVHD by Month 24. To be considered evaluable for the primary safety endpoint, subjects must have either experienced the event by Month 24 (Rel Day 730) or have been followed for at least 12 months (Rel Day of DLC ≥365) without GVHD.

Due to the autologous nature of the eli-cel, GVHD is not expected in this study. It is designated the primary safety endpoint mainly for comparisons with CALD subjects who received allo-HSCT, particularly in studies ALD-101 and ALD-103, which will be detailed in the Inter-Study Comparisons SAP. In case of incidences of GVHD in this study, the number and percentage of subjects with the condition will be provided along with the exact 95% CI for the TP set. A separate subject listing will be provided for subjects who experience any GVHD.

4.3.3. Secondary Safety Endpoints

4.3.3.1. Graft-versus-Host Disease (GVHD)

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

- 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 the respective event by Month 24 (≤Rel Day 730), or have been followed for at least 12 months (Rel Day of DLC ≥365) without GVHD.

4.3.3.2. Transplant-Related Mortality

Transplant-related mortality as determined by the Investigator and summarized for the following intervals: from Rel Day 1 through 100 days post-infusion of eli-cel (Rel Day 101) and from Rel Day 1 through 365 days post-infusion of eli-cel (Rel Day 366). The number and percentage of transplant-related deaths as well as the exact 95% CI will be presented for the TP. Evaluable subjects include subjects 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. Engraftment and Loss of Engraftment

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

Neutrophil Engraftment

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. 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 neutrophil engraftment 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 discontinued or were lost to follow-up before Rel Day 43 without achieving NE are considered failures for NE.

Time to NE will be descriptively summarized for the NEP.

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 above. Subjects who discontinued or were lost to follow-up before Rel Day 43 without achieving NE are considered having 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 he meets both of the following conditions:

- Achieved NE by Rel Day 43 as defined above;
- Has sustained decline in ANC to $<0.5\times10^9$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 $<0.5\times10^9$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% CI 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.

Platelet Engraftment

Platelet engraftment (PE) is defined as achieving 3 consecutive unsupported platelet counts of $\geq20\times10^9$ 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 $\geq20\times10^9$ cells/L is the day of platelet engraftment.

The proportion of subjects who achieved platelet engraftment 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 Month 24 Visit) if no platelet engraftment. The time to PE will be descriptively summarized for subjects who achieved PE.

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

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

Subjects with in-patient transplants are defined as subjects who stay in hospital after infusion and achieve NE in hospital; subjects with out-patient transplants 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 hospitalizations with pre-NE admission and post-NE admissions. Hospitalizations with pre-NE admissions include summary of in-patient hospitalization for in-patient transplant and out-patient transplant. Hospitalizations with post- NE admissions 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 Study ALD-102)
- Post-NE to M12 (Rel Day 365)
- Post-NE to M24 (DLC in Study ALD-102)

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

4.3.3.5. Vector-derived replication competent lentivirus (RCL)

RCL is screened for, and if screening test is positive, the more rigorous co-culture assay is used to definitively confirm RCL detection. Number and proportion of subjects with RCL detected by Month 24 will be tabulated if there is more than 1 case. Evaluable subjects include subjects with at least 1 RCL assessment. A listing of all collected data on screening and confirmatory assay will be provided.

4.3.4. Integration Site Analysis and Assessment of Clonal Predominance

Integration site analysis (ISA) will be performed at Visits Month 6, 12, 18, and 24.

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.

Clonal predominance is defined as

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

3. Any single IS-specific VCN from Q-PCR is > 0.5 c/dg

Persistent clonal predominance is defined as: Clonal predominance criteria #1, #2, or #3 met on a specific gene at least two times, anytime during follow-up.

The number and percentage of subjects who meet the clonal predominance and persistent clonal predominance criteria will be summarized.

Details on clonal predominance and persistent clonal predominance assessment are presented as a schematic in Figure 1.

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4.3.5. Subsequent allo-HSCT

The proportion of subjects who undergo subsequent allo-HSCT by Month 24 will be provided along with exact 95% CI for the TP. The evaluable set includes subjects who received subsequent allo-HSCT thus discontinued from the study, or subjects who have been followed for at least 24 months (Rel Day of DLC ≥730 or completed Month 24 Visit) without subsequent allo-HSCT.

4.3.6. Adverse Events (AE)

Overall summary of AE distributions 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. Hematologic abnormalities reported as AEs that were coded to PTs in the Investigations SOC (e.g., platelet count decreased) will be pooled with appropriate terms in the Blood and Lymphatic System SOC (e.g., thrombocytopenia) for tabulation.

Treatment emergent AEs (TEAE) are defined as AEs occurring on 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 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):
  - Human immunodeficiency virus infection: MedDRA High-Level Term (HLT) = Acquired immunodeficiency syndromes, Retroviral infections
  - Autoimmune disease/ Immunogenicity/ long latency hypersensitivity:
    - MedDRA High-Level Group Term = Autoimmune disorders
    - MedDRA HLT = Autoimmunity analyses, Anaemias hemolytic immune

- MedDRA PT = Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Chronic graft versus host disease, Chronic graft versus host disease in intestine, Chronic graft versus host disease in liver, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in lung, Graft versus host disease in skin, Transfusion associated graft versus host disease

– Infections: MedDRA SOC = Infections and Infestations
– Bleeding events: MedDRA Standardised MedDRA Queries (SMQ) = Haemorrhages
– Malignancies: MedDRA SMQ categories = Malignant tumors, Malignant lymphomas, Myelodysplastic syndrome, Blood premalignant disorders.

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, and death. Study period will be included in the listing.

4.3.7. Laboratory Analysis

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

Internationally accepted reference ranges for children as published by the Mayo Clinic and the New England Journal of Medicine 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. 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	
Hematocrit	White blood cell (WBC) count with differential
Hemoglobin	Platelet count
Red blood cell (RBC) count	
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
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 ICF to < M, M to < C, C to < NE, NE to M12, and > M12 to M24.

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, dried blood spot collection, lumbar puncture and additional lab tests will be listed, separately.

4.3.8. Vital Signs and Physical Examinations

4.3.8.1. 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.

4.3.8.2. 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 screening and at each subsequent visits as noted in the SOE of the Protocol. All physical examination findings will be presented in a subject level listing.

4.3.9. Echo- and electro-cardiograms

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

4.3.10. Concomitant Medications and Procedures

Medications will be coded using the WHO Drug Dictionary.

Medications will be assigned to one or more study periods of the following study periods as defined in Section 3.6.

Concomitant medications will be summarized by the anatomic therapeutic class (ATC) and preferred term for each of the above four 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.

4.4. Exploratory Endpoint Analyses

CCI [redacted]

CCI

CCI

CCI

5. APPENDIX. CLINICAL CALCULATIONS FOR MULTIPLE ELI- CEL LOTS PER SUBJECT

In cases of multiple eli-cel lots per subject is available, weighed eli-cel VCN and %LVV values will be derived using the following formula (example for 2 multiple lots):

- VCN in eli-cel (weighted average per subject; c/dg) =

  [(eli-cel Dose Lot 1/total dose)*(eli-cel VCN Lot 1)] + [(eli-cel Dose Lot 2/total dose)*(eli-cel VCN Lot 2)]

- %LVV+ cells in eli-cel (weighted average per subject) =

  [(eli-cel Dose Lot 1/total dose)*(%LVV Lot 1)] + [(eli-cel Dose Lot 2/total dose)*(%LVV Lot 2)]

- Ratio of eli-cel VCN/eli-cel %LVV+ Cells (weighted average per subject) =

  [[(eli-cel Dose Lot 1/total dose)*(Lot 1 eli-cel VCN/%LVV))] + [(eli-cel Dose Lot 2/total dose)*(Lot 2 eli-cel VCN/%LVV)]]*100

6. CHANGES TO PLANNED ANALYSES

The statistical analyses described in this SAP include modifications to the approach specified in the study Protocol. Such modifications are summarized in Table 5.

Table 5: Changes to Planned Analyses

Specified in Protocol version 10.0	Specified in this SAP
Section 6.1: "Study Day 0 is defined as the day of infusion (transplant)."	Section 3.4: "Rel Day" is defined such that "Rel Day 1 (or Day 1)" is the day of eli-cel infusion, which is CDISC compliant.

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