STATISTICAL ANALYSIS PLAN

Protocol Title:	HLA Typing and Tumor Neoantigen Identification for a Phase I/II Study of Autologous T-Cell Receptor-Engineered T cells (TCR-T) Reactive Against Cancer-specific Mutations in Subjects with Solid Tumors
Protocol Number:	TCR001-201
Short Title:	HLA Typing and Tumor Neoantigen Identification for a Phase I/II Study of Autologous T-Cell Receptor-Engineered T cells (TCR-T) Reactive Against Cancer-specific Mutations in Subjects with Solid Tumors
Sponsor Name:	Alaunos Therapeutics, Inc
Legal Registered Address:	[redacted]
Regulatory Agency Identifier Number(s):	IND 027220
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SIGNATURE PAGE

The following signature indicates that the statistical analysis plan has been approved.

_____ Date: _____

[redacted]
Alaunos Therapeutics, Inc.

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study TCR001-201 is based on the protocol dated 24 Oct 2022.

SAP Version	Date	Change	Rationale
1.0	02-August-2025	Not Applicable	Original

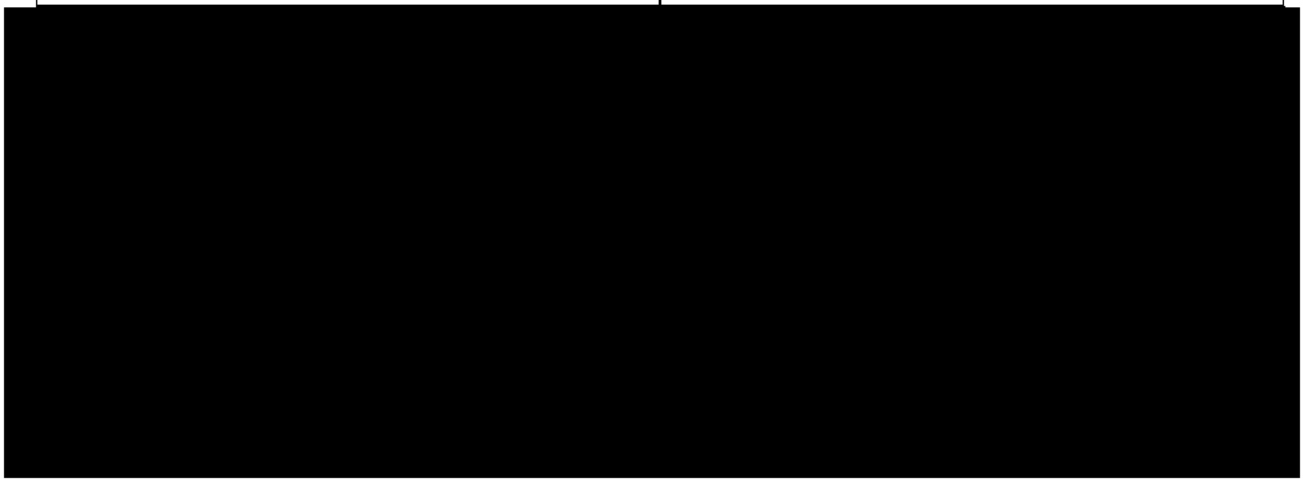
1. INTRODUCTION

The study was closed on 14 Aug 2023 for business reasons after 8 subjects received treatment in Arm A. No formal statistical hypothesis testing will be performed; analyses are descriptive. The Phase I, single-arm (Arm B), dose-escalation portion was not conducted.

This Statistical Analysis Plan (SAP) describes the analyses of safety, efficacy, and immunogenicity data.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase I: • To define the incidence of DLTs and the MTD or RP2D of T-Cell Receptor T cells (herein referred to as TCR-T cell drug product administered without IL-2 (Arm A). Note: this objective was not met due to the early study closure. • Arm A: To define the incidence of DLT and the MTD of TCR-T cell drug product delivered as a single administration.	Phase I: • Number of DLTs and AEs: Neurotoxicity and cytokine release syndrome events will be assessed according to the ASTCT criteria. • All other AEs will be as assessed by the NCI CTCAE (Version 5.0). • Frequency, relatedness, severity, and duration of treatment emergent and treatment related AEs (NCI CTCAE Version 5.0).
Secondary	
Phase I: • To evaluate the feasibility of TCR-T cell drug product manufacturing. • To investigate translational hypotheses related to TCR-T cell persistence without IL-2 (Arm A).	Phase I: • Final T cell count, including percent viability, for appropriate clinical dose. • Duration of TCR-T cell drug product persistence by VCN.



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HLA = human leukocyte antigen; [redacted] MTD = maximum tolerated dose; NCI = National Cancer Institute; [redacted]; RP2D = recommended Phase 2 dose; TCR = T-cell receptor; VCN = vector copy number.

1.2. Study Design

This study was a Phase I/II only Phase 1 of the study was conducted of autologous T cells engineered using the Sleeping Beauty [redacted] system to express T-cell receptors (TCRs) reactive against neoantigens in subjects with solid tumors.

Subjects who have completed initial assessment under the HLA Typing and Tumor Neoantigen Identification Protocol (TCR001-002) (i.e., subjects for whom a TCR matching the subject's somatic mutation[s] and human leukocyte antigen [HLA]-type restriction combination is available in Alaunos Therapeutics Inc.'s [Alaunos] clinical TCR library and have progressive or recurrent disease following standard chemotherapy or standard systemic therapy or were intolerant to previous treatment) will be eligible for enrollment on this study. Subjects will be enrolled into subgroups according to the tumor types listed in Table 1.

Table 1: Tumor Type Subgroups

Subgroup	Tumor Type
1a	Ovarian
1b	Endometrial
2	Colorectal
3	Pancreatic
4	Non-small cell lung cancer
5	Cholangiocarcinoma
1a	Ovarian

1.2.1. Phase I Dose Escalation

The Phase I part of this study is a prospective, open-label, dose-escalation study of TCR-T cell drug product in patients with progressive or recurrent solid tumors who have failed standard therapy. This study utilizes a Bayesian optimal interval design (BOIN) with an accelerated dose escalation to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of TCR-T cell drug product. Subjects who fulfill the eligibility criteria will receive a single infusion of TCR-T cell drug product at the assigned dose level on Day 0. Safety and pharmacokinetic (PK) profiles, and the preliminary efficacy will be examined for each dose level.

The study starts with screening of subjects for treatment with TCR-T cell drug product (Arm A) at Dose Level 1 (DL1). This dose level will follow an accelerated dose escalation and is planned to treat one subject at dose level 1 in the absence of a dose-limiting toxicity (DLT). After the subject completes the DLT period (Day 0 to Day 28), the subject will be evaluated for toxicities. If the first subject experiences a DLT, 3 additional subjects will be enrolled and treated at DL1 before escalating to dose level 2 (DL2). If the first subject does not have a DLT(s), the subsequently patients will be enrolled, and dosed at the next higher dose level (DL2) per the BOIN design. At least 2-3 subjects will be enrolled at DL2 to enable evaluation of TCR-T cell persistence data by the Safety Review Committee (SRC).

For the initial two subjects of Arm A there will be a dose staggering interval of 28 days. Dose administration for the subsequent subjects will not occur until the initial 2 subjects have completed their safety evaluation for dose-limiting toxicities.

There are 2 dose escalation stopping rules in this BOIN study.

- Stop the trial if the lowest dose is eliminated due to overt toxicities;
- Stop the dose escalation and estimate the MTD/RP2D if the number of new subjects treated at the current dose level reaches 9.

The duration of this study from the time of initiating screening until the completion of survival follow up is anticipated to be approximately 25 months.

Subjects will be lymphodepleted 7 days prior to TCR-T cell drug product infusion. If the TCR-T cell drug product infusion is delayed > 2 weeks, lymphodepletion must be repeated, unless otherwise agreed between the Investigator and Alaunos's Medical Monitor or designee.

Pre-medication is recommended approximately 30 minutes prior to TCR-T cell drug product infusion and will include acetaminophen 650-1000 mg orally and diphenhydramine 12.5 mg intravenously (IV) or 25 to 50 mg orally (or equivalent). Alternatively, subjects can be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within 30 to 60 minutes prior to infusion. Corticosteroids should not be used as a pre-medication at any time except in the case of an emergency.

TCR-T intended dose and dose range are shown in Table 2.

Table 2: TCR-T Dose Levels (Intended Dose and Dose Range)

Dose Level	TCR^+ Cells	Minimum	Maximum
DL-1	$<1.0 \times 10^9$	NA	$<1.0 \times 10^9$
DL1	5×10^9	1.0×10^9	$<10 \times 10^9$
DL2	40×10^9	10×10^9	$<70 \times 10^9$
DL3	100×10^9	70×10^9	150×10^9
DL-1	$<1.0 \times 10^9$	NA	$<1.0 \times 10^9$

DL = Dose Level; NA = not applicable; TCR = T cell receptor.

This study includes Screening, Pre-Treatment, Treatment and Follow-up Periods. The screening period is from the time the subject signs the informed consent form (ICF) until the subject is deemed eligible by the Medical Monitor. The Pre-Treatment Period starts when the Screening period ends.

The study will be paused and further investigation initiated if:

- Occurrence of Grade 4 DLTs in 2 subjects at any time during the conduct of the study trial;
- 1 treatment-related death occurs after the administration of TCR-T cell drug product;
- Death not related to disease progression;
- Development of a secondary malignancy, Epstein-Barr virus (EBV) lymphoma or polyclonal lymphoproliferative disease (PLPD) in an EBV negative subject. Note: accrual of EBV positive subjects will be halted if this is observed.

1.2.2. Dose-Limiting Toxicities

A DLT is a study intervention-related AE occurring within the DLT window (Day 0 to Day 28 days post TCR-T cell drug product infusion), defined based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as the following:

Hematologic

- Grade 4 neutropenia lasting ≥ 14 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding,
- ≥ Grade 3 febrile neutropenia associated with hemodynamic compromise or objective evidence of infection.

Non-hematologic

- Cytokine release syndrome (CRS) Grade 3 or 4 that does not improve to Grade ≤ 2 within 72 hours despite appropriate treatment.
- Grade 3 immune-effector cell-associated neurotoxicity syndrome (ICANS) that does not return to grade ≤2 or lower within 7 days.
- Any Grade 5 adverse event (not due to disease progression or to a known cause other than TCR-T (e.g., automobile accident)).
- Grade 3 hepatic toxicity that does not return to Grade ≤ 2 or lower within 7 days.
- Grade 3 toxicity involving vital organs that does not improve to Grade ≤ 2 or lower within 7 days of onset.
- Grade 4 toxicity not previously specified.

In addition to the related AEs mentioned above, any related Grade 3 toxicity and all Grade 4 toxicities will be considered DLTs except the following:

- Grade 3 anemia that is not associated with other clinically significant complications
- Expected chemotherapy toxicities due to lymphodepletion including cytopenias, fludarabine related adverse reactions, and cyclophosphamide related hemorrhagic cystitis.

1.2.3. Pre-Treatment Period

Subjects will undergo an apheresis [redacted] a minimum of 30 days prior to planned TCR-T cell drug product infusion. Bridging therapy after apheresis will be allowed following consultation with the Alaunos Medical Monitor. Subjects who have sufficient lymphodepletion from bridging therapy do not need additional lymphodepletion prior to infusion of TCR-T cell drug product.

1.2.4. During the Treatment Period

Lymphodepletion, if needed, with cyclophosphamide and fludarabine will proceed after confirmation of enrollment. After the lymphodepleting regimen, TCR-T cell drug product will be administered to the subject by infusion on Day 0 at the subject's assigned dose level.

1.2.5. The Follow Up Period

This period will begin after the subject completes their Day 28 visit. In the Follow-up Period, clinical and radiologic response will be evaluated at 6 and 12 weeks after TCR-T cell drug product infusion and every 12 weeks thereafter until they complete the 2-year follow-up period or discontinue from this study (e.g., due to disease progression, initiation of new anti-cancer therapy, withdraw consent, etc.), whichever occurs first. Enrollment into the long term follow up study (below) will occur after completion or discontinuation from this study.

The schedule of assessments is provided in Table 10 and Table 11 of the protocol.

1.2.6. Duration of The Study

The duration of accrual from the time of initiating subject enrollment until the completion of survival follow-up is anticipated to be approximately 7 years.

The overall duration is expected to be up to 2 years and 1 month for an individual subject, including the following:

- Screening period of up to 2 weeks
- Study treatment period of approximately 5 weeks (Days -7 through Day 28)
- The Follow-up Period includes assessment of tumor response at 6 weeks (± 1 week), and then every 3 months (± 2 weeks) for up to two-years post-TCR-T cell drug product infusion.

In addition, subjects who receive investigational product without objective evidence of disease progression during the 2-year follow-up period will continue to be followed until progression has been documented via the Long-Term Follow-Up protocol (TCR001-202).

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses are being tested. Statistical analyses will be concentrated on selection of the MTD or RP2D dose.

3. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined in Table 3.

Table 3: Description of Analysis Sets

Enrolled Analysis Set (ENR)	The ENR will consist of all participants who have received lymphodepletion.
Full Analysis Set (FAS)	The FAS will consist of ENR participants who received a TCR-T cell drug product infusion and have at least one valid post-baseline assessment (PK, PD, efficacy).
Safety Analysis Set (SAF)	The SAF will consist of ENR participants who received a TCR-T cell drug product infusion.
Per Protocol Analysis Set (PPS)	The PPS consists of SAF participants who do not have major treatment protocol violation during the DLT observation period. Participants with major treatment deviations during DLT observation period unrelated to safety or tolerability events are not evaluable for the dose-escalation assessment and will be replaced as needed.
Dose Determining Analysis Set (DDS)	The DDS will consist of PPS participants who have completed the planned TCR-T cell drug product infusion and experienced a DLT or completed the DLT observation period.

DLT = dose-limiting toxicity; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TCR = T cell receptor.

Data summaries to be presented on SAF, FAS, and PPS will only be produced on each analysis set if the population groups are not identical.

All safety summaries will be evaluated using the SAF except the evaluation of DLT and the determination of the MTD which will be evaluated using the DDS. Safety analyses includes: extent to exposure, all AE analysis including serious adverse events (SAEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and echocardiogram results, etc. All efficacy summaries will be based on the FAS and PPS. A data listing of subjects excluded from the FAS, SAF, DDS to include the reason for exclusion, will be presented.

4. STATISTICAL ANALYSES

4.1. General Considerations

Statistical analyses will be reported with tables, figures, and listings and using recommended International Council on Harmonisation (ICH) numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (Apr 2003).

Data from all participating investigational sites will be pooled prior to analysis.

Baseline is defined as the most recent non-missing assessments (at scheduled or unscheduled visit) collected prior to the first dose of study drug in the study. The following situations are specified.

If subjects have no value as defined above, then the baseline results will be considered missing.

All participant data up to the end of study (EOS)/completion or to early termination/withdrawal from study will be included in the analyses, regardless of treatment status and respective of applicable analyses set. In general, there will be no imputation for missing data, with the exception of missing date of adverse events and concomitant medications, and non-compartmental PK analysis, where concentration values below the limit of quantification (BLQ) occurring prior to the first measurable concentration will be set to zero.

All available data will be summarized over specified intervals (e.g., visits, days, treatment cycles) from start of treatment until withdrawal from study using summary statistics.

Deviations from the original, planned analyses will be documented in the final study report.

4.1.1. Reporting Conventions

All data processing, summarization, and analyses will be performed using SAS®. All data are electronically formatted in order to follow Clinical Data Interchange Standards Consortium (CDISC) All SAS programs will be independently validated per the validation standard operating procedure.

Unless specified otherwise, data will be displayed using the following study phases, treatment group, and 6 disease-specific dose cohort labels if applicable.

- Phase I Dose Escalation
- Ovarian
- Endometrial
- Colorectal
- Pancreatic
- Non-small cell lung cancer
- Cholangiocarcinoma
- [redacted]
- $<1.0 \times 10^9$

- 5×10^9
- 40×10^9
- 100×10^9

Tables and figures will be summarized by dose cohort, visits, days if applies, and tables will also include a column for all participants combined. In general, data collected and any derived data will be presented in participant data listings for all enrolled participants. Listings will be ordered by site, participant number, dose cohort, visit, and assessment or event date, days relative to the first dose date. The dose cohort presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of participants with available data (n), mean, standard deviation (SD), median, first (Q1) and third (Q3) quartiles, minimum (only for survival analysis), and maximum values. For PK/PD parameters, the following statistics will be displayed: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV, median, minimum, and maximum. Geometric mean and coefficient of variation will not be calculated for t_{max} or t_{last}. Categorical variables will be summarized by the population size (N), number of participants with available data (n), number of participants in each category, and the percentage of participants in each category. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with non-missing data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of participants in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., confidence intervals [CIs]) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare dose cohorts.

Descriptive statistics will be tabulated by dose cohort and reviewed to evaluate all study endpoints.

4.1.2. Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. Data collected for the last participant visit completed will be summarized separately for:

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). Data from unscheduled visits will be included in subject listings.

4.1.3. Data Handling Rules

Data will display on participant listings to include the sign.

4.1.4. Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on participant data listings, where study day will be determined as:

- The assessment/event date minus the start date, if the assessment/event date is prior to the start date; and
- The assessment/event date minus the start date, plus one, if the assessment/event date is on or after the start date.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
  - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study intervention; or
  - Later date – earlier date, if the earlier date is prior to the date of first dose of study intervention.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.
- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

Partial dates for AEs and concomitant medications will be imputed to determine onset or stop dates following the rules as specified in Appendix 2 (Section 6.2). Imputed data for dates can only be used in preparation of derived datasets. Original partial dates, instead of imputed dates,

will be displayed in listings. Study day relative to the first dose of study drug associated with missing or partial dates will not be displayed in AE listings.

Dates will be displayed as DDMMMYYYY.

4.2. Participant Dispositions

Participant disposition will be summarized for the ENR population and over all participants combined. Summaries will include the number and percentage of participants in each analysis set,

Subjects that are in the ENR population but not enrolled will be summarized by reason for screen failure. The number of subjects will be summarized for the following analysis population:

- Enrolled population
- Safety Analysis Set
- Full Analysis Set
- Dose Determining Analysis Set
- Per-Protocol Analysis Set

Reasons for discontinuation will be summarized for the pre-treatment period (from apheresis to prior to lymphodepleting [LD] chemotherapy), treatment period (from LD chemotherapy to prior to TCR-T infusion) for enrolled population and post-treatment follow-up period for the safety population after initial TCR-T infusion. In addition, the following categories will be summarized:

- Subjects who discontinued the study
- Subjects who are still ongoing in the study
- Subjects who are enrolled in the long term follow up study

Subject disposition mentioned above will be summarized by treatment $<1.0 \times 10^9$, 5×10^9, 40×10^9, 100×10^9.

4.3. Demographic and Baseline Characteristics

4.3.1. Demographic and Baseline Characteristics

Demographic (age, sex, and race) and baseline characteristics will be summarized descriptively using the SAF population by treatment group, disease specific dose cohort and overall. Baseline characteristics include the following:

- Age (years) and age group (<65 and ≥ 65)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- Body surface area (BSA)
- Childbearing potential
- HLA
- Primary Cancer Type
- Type of Gynecological Cancer
- Bridging Therapy
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

A listing of these data will be provided.

Medical history, prior therapy, concomitant medications will be summarized by treatment, disease group and overall, as applicable.

4.3.2. Baseline Tumor Characteristics

Baseline tumor characteristics will be summarized using SAF, FAS and PPS by treatment group, disease group and overall.

- Sum of longest diameter for the target lesion (shortest for lymph nodes) at Baseline
- Largest single target lesion
- Sites of metastases
- Number of sites of metastases

A listing of these data will be provided.

4.3.3. Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment group, disease group and overall total for cancer history at study entry and at diagnosis.

- Ovarian/Endometrial/Colorectal/Pancreatic/Non-small cell lung cancer/Cholangiocarcinoma, Cancer History at Study Entry
- Ovarian/Endometrial/Colorectal/Pancreatic/Non-small cell lung cancer/Cholangiocarcinoma, Cancer History at Diagnosis
- Time Since Initial Diagnosis (Month)

A listing of these data will be provided.

4.3.4. Prior Therapy and Surgeries

Descriptive statistics of prior therapies by treatment, disease group, and overall will be summarized for SAF population.

- Radiotherapy
- Systemic Anti-Cancer Therapy
- Cancer Surgeries or Procedures

A listing of these data will be provided.

4.3.5. Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities® (MedDRA).

4.3.6. Treatment Plan

An overview of the treatment schedule is shown below.

Table 4: Treatment Schedule

Lymphodepletion Day	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**				
TCR-T Cell Infusion Day								**0**	**1**	**2**	**3**
Cyclophosphamide (60 mg/kg) [1,2]	X	X									
Mesna3	X	X									
Fludarabine (25 mg/m) [1,2]	X	X	X	X	X						
TCR-T cell drug product								X			
Cyclophosphamide (60 mg/kg) [1,2]	X	X									
Mesna[3]	X	X									

1. At the discretion of the investigator in heavily pre-treated or irradiated subjects who are expected to have lower bone marrow reserve, a lower dose regimen of Cyclophosphamide 30 mg/kg /Fludarabine 25 mg/m^2 may be administered
2. In the event the patient had previous intolerance to cyclophosphamide or due to supply issues, bendamustine 90 mg/m^2/day for 2 days or bendamustine 70 mg/m2/day + fludarabine 30 mg/m2/day for 3 days may be substituted with approval from the Alaunos Medical Monitor.
3. Mesna should be administered according to institutional procedure.

4.3.6.1. Lymphodepletion (LD) Chemotherapy

Details of exposure to lymphodepletion chemotherapies will be presented for treatments. The summary will be also presented for whether the dose was administered, reasons if not administered, whether the dose was adjusted along with reason for dose interruption/reduction using number of subjects and percentages.

Descriptive statistics will be provided for the number of days dosed, duration of study medication (including interruption), total cumulative dose, actual daily dose, actual daily dose by body surface area. The overdose will also be summarized if applicable.

The listings of lymphodepletion chemotherapies for individual subjects will also be provided.

4.3.6.2. TCR-T Cell Drug Product

Exposure of TCR-T cell drug product will be summarized by dose cohort and the summary of TCR-T dose adjustment including whether the infusion was interrupted along with the reasons for dose interruption.

4.4. Primary Endpoint(s) Analysis

The primary endpoints will be summarized as below for Phase I:

Number of DLTs and AEs: Neurotoxicity and cytokine release syndrome events will be assessed according to the ASTCT criteria.

All other AEs will be as assessed by the NCI CTCAE (Version 5.0).

Frequency, relatedness, severity, and duration of treatment emergent and treatment related AEs (NCI CTCAE Version 5.0).

4.4.1. Phase I: Incidence of Dose Limiting Toxicities

4.4.1.1. Definition of Dose Limiting Toxicity

A DLT is a study intervention related AE occurring within the DLT window (Day 0 to Day 28 days post TCR-T cell drug product infusion), defined based on NCI CTCAE Version 5. Grade 3 anemia that is not associated with other clinically significant complications.

4.4.1.2. Analytical Approach

The participant incidence of DLTs by MedDRA PT will be presented using the same methodology as described in Section 4.4.2 of this SAP.

4.4.2. Phase I: Incidence of Treatment-Emergent Adverse Events

4.4.2.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as those AEs with onset after the first dose of study treatment or existing events that worsened after the first dose during the study, and within 28 days after last treatment date.

4.4.2.2. Cytokine Release Syndrome

For the purpose of this study, the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus guidelines should be used for grading of cytokine release syndrome (Lee 2019).

A single PT term—Cytokine Release Syndrome—as recorded on the AE CRF will be summarized. Summaries will include number of subjects who reported CRS, maximum toxicity grade of CRS, time to onset of CRS, duration of CRS, and treatment for CRS.

The same analysis will be performed for the Grade 3 or higher CRS events.

CRS signs or symptoms will also be summarized by SOC, PT, and maximum CTCAE grade.

4.4.2.3. Neurotoxicity

Immune effector cell (IEC) therapy may result in neurotoxicity, termed IEC-associated neurotoxicity syndrome (ICANS). ICANS may include symptoms such as confusion, aphasia, seizure, and/or cerebral edema. The ASTCT Consensus guidelines should be used for the grading and management of immune effector cell- associated neurotoxicity syndrome (Lee 2019).

All PTs within the primary or secondary SOCs of Nervous System Disorder and Psychiatric Disorder.

- Selected PTs of neurologic toxicity events as determined by Sponsor.

4.4.2.4. Other Treatment Emergent Adverse Event

All TEAEs will be summarized as follows at treatment group and overall.

- All TEAEs
- All Grade 3/4/5 TEAEs
- All treatment-related TEAEs
- All treatment-related Grade 3/4/5 TEAEs
- All Serious TEAEs
- All treatment-related Serious TEAEs

For TEAEs with a missing or partial start date, if there is no evidence that the AE started (or worsened) before the first dose date, the start date will be imputed to the first dose date.

Adverse events with a missing severity will be presented in the summary table as a severity category of "Missing." Adverse events with a missing relationship to study drug will be presented in the summary table as "Definitely" related to study drug. The imputed values for relationship to study drug will be used for incidence summaries, while actual values will be presented in data listings.

The number and percentage of subjects reporting each TEAE will be summarized by SOC and PT using the SAF. Tables will be sorted in descending order of frequencies in total by SOC. Preferred terms will be sorted by descending in overall total within SOC. The following summaries will be produced:

- TEAEs, by SOC and PT
- TEAEs, by SOC, PT and Severity
- TEAEs by PT
- TEAEs by relationship to study drug by SOC, PT
- TEAEs related to study drug by SOC, PT and Severity
- TEAEs related to study drug by PT
- Grade ≥3 TEAEs by SOC, PT and Severity
- Grade ≥3 TEAEs related to study drug by SOC, PT and Severity

- Serious TEAEs by SOC, PT
- Serious TEAEs by SOC, PT and Severity
- Serious TEAEs by PT
- Serious TEAEs related to study drug by SOC, PT and Severity
- AEs resulting in dose modification by preferred terms
- AEs resulting in treatment discontinuation will be summarized

TEAEs will be summarized by relationship to treatment as Related, Not related, Not Applicable.

4.4.2.5. Death

Primary cause of death will be summarized by category and by SOC and PT.

An additional summary will include all deaths observed for enrolled population, for the periods of apheresis to LD chemotherapy, LD chemotherapy to TCR-T infusion, and on or after TCR-T infusion.

Listings will be provided and will include all subjects who died after enrollment.

All AEs will be presented in subject data listings. In addition, listings of DLTs, SAEs, AEs leading to death, and AEs leading to dose modification and discontinuation from treatment will be provided.

[redacted]

4.5. Secondary Endpoint(s) Analysis

The secondary endpoints will be summarized as below for Phase I:

- Final T cell count, including percent viability, for appropriate clinical dose.
- Duration of TCR-T cell drug product persistence by vector copy number (VCN).

4.5.1. Phase I: Final T Cell Count

4.5.1.1. Definition of Final T Cell Count

Determined from final certificate of analysis.

4.5.1.2. Main Analytical Approach

Frequency count will be provided for final T cell count. Descriptive statistics will be provided. In addition, frequency counts of actual final T cell count in the following categories will be presented.

4.5.2. Phase I: Duration of TCR-T Cell Persistence by Vector Copy Number

Duration of persistence of TCR-T cell drug product by VCN is defined as the length of time from the date of infusion of TCR-T cell product to the date of the last measurable (i.e., ≥ limit of quantification [LOQ]) TCR-T cell level by VCN.

Descriptive statistics will be presented for duration of persistence. A frequency count by category

[redacted]

4.7. Other Safety Analysis

4.7.1. Laboratory Results

The following summaries will be generated separately for hematology, serum chemistry, urinalysis.

4.7.1.1. Classification of Laboratory Results

Laboratory results will be classified according to NCI CTCAE, Version 5.0. Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics. Observed and change from baseline results are summarized at scheduled visits. For all quantitative laboratory parameters, the observed values and the change from baseline to each post baseline visit, to the end of treatment (defined as the last on-treatment value) and end of study will be summarized by visit. Qualitative parameters will be summarized using frequencies (number and percentage of subjects). Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Newly Occurring on-Treatment CTCAE Grade 3 or 4: A summary of the number and percentages of subjects with newly occurring on-treatment laboratory CTCAE Grade ≥3 will be generated for each lab parameter at all visits.

Shift Tables from Baseline to Worst CTCAE Grade: Shift tables from baseline to worst CTCAE grade will also be generated for selected parameters. The highest grade will be assigned for a laboratory finding for more than 1 grade level. For each selected laboratory parameter, the percentages will be based on the number of subjects with non-missing measurements at any visits.

Patient listing of laboratory values and grading will be provided by laboratory parameter and dose level. The incidence of lab abnormalities will be shown by parameter, dose level and overall.

4.7.1.2. Clinically Significant Abnormal

All laboratory tests with values considered clinically significantly abnormal during participation in the study. Shift tables clinically significantly from baseline to study visits will also be generated for selected parameters.

A listing will be provided, including toxicity grade, normal range, and DLT.

4.7.2. Vital Signs

Vital sign parameters collected during the study include weight, BSA, systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and body temperature (°C), and Oxygen Saturation Observed values and the corresponding change from baseline will be summarized at scheduled nominal visit by treatment and disease group.

4.7.3. Electrocardiograms

Descriptive statistics for ECG parameters (i.e., QTcF, QRS, RR, PR, QT, and heart rate) and changes from baseline will be summarized over time. Shift tables will present changes from

baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment (EOT).

In addition, the number (percentage) of subjects with at least 1 post baseline abnormal ECG result in QTcF will be summarized. Clinically abnormal ECG results will be categorized

4.7.4. Echocardiograms/MUGA

Echocardiograms (or multi-gated acquisition [MUGA] scans) will be performed at screening and asclinically indicated during the study.

The percent (%) of left ventricular ejection fraction (LVEF) will be summarized by descriptive statistics. Number and percentage of Normal, Abnormal, Not Clinically Significant, Abnormal, Clinically Significant will be presented by treatment and disease group.

A listing will be provided.

4.7.5. Physical Exam

A complete physical examination will include assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be collected.

Number and percentage of Normal, Abnormal, Not Clinically Significant, Abnormal, Clinically Significant will be presented by treatment and disease group.

A listing will be provided.

4.9. Interim Analyses

The design lays out a pre-defined interim analysis allowing for stopping tumor type enrollment for futility to limit undue exposure for unacceptable treatments.

5. SAMPLE SIZE DETERMINATION

5.1. Dose Escalation

Originally, up to 18 subjects will be treated across all dose levels. The design (Liu & Yuan, 2015; Yuan 2016) will be used to find the MTD. Eight subjects were treated before early closure. No power calculations are applicable; analyses are descriptive.

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 12. We will enroll and treat patients in dose dose cohorts of size 3. DLTs are defined in Section 5.3 in the protocol, and only those DLTs that occur within the first cycle will be used for dose finding. The BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.253, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is > 0.359, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $Pr(p\_j > 0.3 \mid data) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j,j= 1,⋯, 4. This posterior probability is evaluated based on the beta-binomial model y_j|p_j~binomial(p_j) with p_j~uniform(0,1), where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate <=1/6, a dose with 2/3 patients experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 1 in the protocol, which will be used to conduct the trial.

The steps to implement the BOIN design are described as follows:

1. Perform accelerated titration as follows. Treat the first patient at DL2 and escalate the dose in the one-patient-per-dose-level fashion until any of the following events is observed: (i) the first instance of DLT, (ii) the second instance of moderate (Grade 2) toxicity, or (iii) the highest dose level is reached. Then, treat 2 additional subjects at the current dose level. Hereafter, subjects are treated in dose cohorts of size 3 as described in Steps 2 and 3.
2. To assign a dose to the next dose cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 5. When using Table 5, please note the following:
    a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.

c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat Step 2 until the maximum sample size of 12 is reached, or stop the trial if the number of evaluable patients treated at the current dose reaches 9 and the decision according to Table 5 is to stay at the current dose.

Table 5: Dose Escalation/De-escalation Rule for the BOIN Design

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Number of evaluable patients treated at current dose	1	2	3	4	5	6	7	8	9
Escalate if # of DLT <=	0	0	0	1	1	1	1	2	2
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5

Note: "# of DLT" is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next dose dose cohort of patients. "NA" means that a dose cannot be eliminated before treating 3 evaluable patients.

After the trial is completed, select the MTD based on isotonic regression as specified in (Liu & Yuan, 2015). This computation is implemented by the shiny app available at http://www.trialdesign.org. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

Abbreviation or Specialist Term	Term
AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomic Therapeutic Chemical
BLQ	below the limit of quantification
BOIN	Bayesian optimal interval design
BOR	best overall response
BMI	body mass index
BSA	body surface area
CD	cluster of differentiation
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DDS	Dose Determining Analysis Set
DL1	Dose Level 1
DL2	Dose Level 2
DLT	dose-limiting toxicity
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ENR	Enrolled Analysis Set

Abbreviation or Specialist Term	Term
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
ICANS	immune-effector cell-associated neurotoxicity syndrome
ICH	International Council on Harmonisation
IEC	immune effector cell
IL-2	interleukin-2
[redacted]	[redacted]
IV	intravenous(ly)
LD	lymphodepletion(ing)
LOQ	limit of quantification
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerate dose
MUGA	multi-gated acquisition
N or n	sample size or number of participants
NCI	National Cancer Institute
next-generation sequencing	next-generation sequencing
NK	natural killer (cells)
ORR	objective response rate
[redacted]	[redacted]
PD	progressive disease or pharmacodynamic(s)
PLPD	polyclonal lymphoproliferative disease
PK	pharmacokinetic(s)
PPS	Per Protocol Analysis Set
PR	partial response
PT	preferred term

Abbreviation or Specialist Term	Term
[redacted]	[redacted]
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	stable disease or standard deviation
SOC	system organ class
SRC	Safety Review Committee
TCR	T-cell receptor
TCR-T	T-cell receptor engineered T cell
TEAE	treatment-emergent adverse event
TTF	time to treatment failure
uCR	unconfirmed complete response
uPR	unconfirmed partial response
VCN	vector copy number
WHODDE	World Health Organization Drug Dictionary Enhanced

6.2. Appendix 2: Imputation Rules for Missing AE or Concomitant, Medication Dates

Imputation rules for missing or partial AE or concomitant medications are defined as follows:

<table>
<tr><td colspan="3">AE and concomitant medication</td></tr>
<tr><td colspan="2">Scenario</td><td rowspan="2"></td></tr>
<tr><td>Onset date</td><td>Stop date</td><td>Imputation rule</td></tr>
<tr><td>Partially Missing</td><td>Complete Date</td><td>Imputation of <u>onset</u> date:
A. If partial date has day and month missing:
i) If year of the partial date < year of the first dose date, assign December 31st to the missing fields.
ii) If year of the partial date = year of the first dose date, assign the first dose date to the missing fields.
iii) If year of the partial date > year of the first dose date, assign January 1st to the missing fields.
Note: if first dose date is missing, then use randomization date in the above imputations.
B. If partial date has missing day only:
i) If the month and year of the partial date < month and year of the first dose date, assign last day of the onset month to the missing day.
ii) If the month and year of the partial date = month and year of the first dose date, assign the day of first dose to the missing day.
iii) If the month and year of the partial date > month and year of the first dose date, assign first day of the onset month to the missing day.
iv) If the imputed onset date (after A or B above) is after the stop date, the onset date will be imputed to be equal to the stop date.</td></tr>
<tr><td>Complete Date</td><td>Partially Missing</td><td>Imputation of <u>stop</u> date (if not reported as ongoing):
C. If partial date has day and month missing:
i) If year of partial date < year of the last known alive date (LKAD), assign December 31st to the missing fields.
ii) If year of partial date = year of the LKAD, assign the LKAD date to the missing fields
iii) If year of partial date > year of the LKAD, the missing day and month will NOT be imputed.
D. If partial date has missing day only:
i) If the month and year of the partial data < the month and year of the LKAD, assign the last day of the onset month to the missing day.
ii) If the month and year of the partial date = the month and year of the LKAD, assign the LKAD to the missing day.</td></tr>
</table>

		iii) If the month and year > the month and year of the LKAD, the missing day will NOT be imputed. LKAD is defined as the date of death or the last day recorded on Early Termination/End of Study Visit. iv) If the imputed stop date (after C or D above) is before the onset date, the stop date will be imputed to be equal to the onset date.
Partially Missing	Partially Missing	Impute onset date per A and B above Impute stop date (if not reported as ongoing) per C and D If imputed onset date > imputed stop date, then set onset date = stop date = minimum of (imputed onset date per A and B, imputed stop date per C and D)
Partially Missing	Completely Missing	Impute onset date per A and B above. Impute stop date (if not reported as ongoing) as the LKAD; see definition above. If imputed onset date > imputed stop date, assign onset date = stop date = minimum of (imputed onset date per A and B, imputed stop date above)
Adverse Events		
Completely Missing	Partially Missing	Impute onset date as the first dose date; if first dose date is missing, then use randomization date Impute stop date (if not reported as ongoing) per C and D above If imputed onset date > imputed stop date, then set onset date = stop date = minimum of (imputed onset date above, imputed stop date per C and D)
Completely Missing	Complete	Impute onset date as the first dose date; if first dose date is missing, then use randomization date. If imputed onset date > stop date, then set onset date = (complete) stop date
Complete Date	Completely Missing	Impute stop date (if not reported as ongoing) as the LKAD; see definition above. If onset date > imputed stop date, then set stop date = (complete) onset date.
Completely Missing	Completely Missing	Impute onset date as the first dose date; if first dose date is missing, then use randomization date. Impute stop date (if not reported as ongoing) as the LKAD; see definition above.
Concomitant Medication		
Completely Missing	Partially Missing	Do not impute onset date Impute stop date (if not reported as ongoing) per C and D above
Completely Missing	Complete	Do not impute onset date.
Complete Date	Completely Missing	Impute stop date (if not reported as ongoing) as the LKAD; see definition above.

		If onset date > imputed stop date, then set stop date = (complete) onset date.
Completely Missing	Completely Missing	Do not impute onset date. Impute stop date (if not reported as ongoing) as the LKAD; see definition above.

6.3. Appendix 3: Baseline Characteristics and Demographics

Demographic and baseline characteristics will be summarized. Demographic (e.g., gender, age, race) and baseline characteristics (e.g., disease status, height, weight, and prior therapy) will be summarized by treatment, disease group and overall, as applicable.

Demographic variables including age, sex, ethnicity and race will be summarized by treatment, disease group and over all participants combined for the SAF, FAS, and DDS. Age will be calculated relative to date of informed consent, as follows:

- If the month and day portion of the informed consent date is prior to the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth, minus one;
- If the month and day portion of the informed consent date is on or after the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of participants in each parameter category.

Baseline characteristics include, height, weight, and body mass index (BMI). Body mass index will be calculated as: BMI = weight (kg) / [height $(cm)^2$ / 10,000].

6.4. Appendix 4: Prior and Concomitant Medications/Procedures/ Surgeries

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE), version March 2023. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (Level 4) and drug name.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study intervention. A concomitant medication is defined as any medication administered on or after the date of the first dose of study intervention. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study intervention dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study intervention dosing, it will be considered concomitant.

For both prior and concomitant medications summaries, the number and percentage of participants receiving any medication will be summarized by treatment and disease group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Prior medications will also be summarized over all participants combined. Participants reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

Concomitant medications will be summarized by c for all medications reported on the Concomitant Medications eCRF. The number and percentage of participants receiving any medication will be summarized, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Participants reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

6.5. Appendix 5: Protocol Deviations

Important protocol deviations will be summarized by disease group and over all participants combined for the FAS. Important protocol deviations are protocol deviations captured on-study that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

All important protocol deviations will be determined and appropriately categorized prior to database lock. The number and percentage of subjects with any important protocol deviations as well as the number and percentage of subjects with violations within each category will presented.

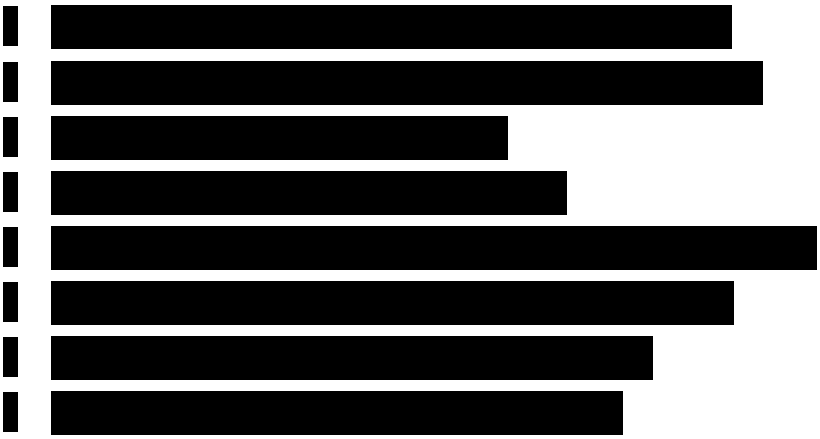
6.6. Appendix 6: Tables, Listings, and Figures Shells

The following standard tables, listings, and figures will be generated as data is available to support the analyses described in this SAP and the final Clinical Study Report. Due to the early closure of the study, not all tables, listings, and figures may be available; these will be noted in the Clinical Study Report.

1. Disposition and Demographics

- Table 14.1.1: Subject Disposition - All Subjects
- Table 14.1.2.1: Demographics and Baseline Characteristics
- Table 14.1.2.2: Baseline Disease Characteristics
- Listing 16.2.1: Subject Disposition
- Listing 16.2.2: Demographic Data

[redacted]



3. Safety Analysis

- Table 14.3.1.1: Overview of Treatment-Emergent Adverse Events
- Table 14.3.1.2: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Table 14.3.1.4: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term
- Table 14.3.1.7: Treatment-Emergent Adverse Events by Maximum Severity (CTCAE)
- Table 14.3.2.1: Deaths - Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Table 14.3.4.1: Summary of Clinical Laboratory Values - Chemistry
- Table 14.3.4.2: Summary of Clinical Laboratory Values - Hematology
- Table 14.3.4.3: Shift Table of Clinical Laboratory Results - Chemistry

- Table 14.3.4.4: Shift Table of Clinical Laboratory Results - Hematology
- Listing 16.2.7: Adverse Events
- Listing 16.2.8: Deaths
- Listing 16.2.9: Concomitant Medications
- Listing 16.2.11.1: Clinical Laboratory Data - Chemistry
- Listing 16.2.11.2: Clinical Laboratory Data - Hematology

4. Exposure and Other Analyses

- Table 14.4.1: Extent of Exposure
- Table 14.5.1: Summary of ECOG Performance Status
- Listing 16.2.4: Dates of Important Events

7. REFERENCES

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