



Statistical Analysis Plan

NCT Number: NCT05164666

Title: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-103 in Adult Patients with Mesothelin-Expressing Advanced or Metastatic Solid Tumors

Study Number: TAK-103-1001

Document Version and Date: Version 2.0 / 10 June 2024

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-103-1001

Study Title: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-103
in Adult Patients with Mesothelin-Expressing Advanced or Metastatic Solid Tumors

Phase: 1

Version: 2.0

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Prepared by: [REDACTED]

Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
2.0	10-Jun-2024	5.3 CK Analysis Set text updated as per Protocol Amendment 4.
		5.6 New section – Immunogenicity-evaluable Analysis Set text added as per Protocol Amendment 4.
		6.1 Text added to classify Subjects Withdrawn from Study Treatment as Discontinued TAK-103 Infusion. Text added to clarify that Mesothelin H-scores will be rounded to the nearest whole number. Text added to clarify that Mesothelin TPS-scores will be rounded to the nearest whole number. Text updated to specify Total CAR-T Cell Number of TAK-103 Administered rather than Administered Dose. Text added to define Total Amount of Conditioning Chemotherapy Converted to BSA.
		6.2.5.2 Text added to include completion status of Study Treatment as an analysis variable.
		6.2.6.2 Immunogenicity-evaluable Analysis Set added to list of Analysis Sets.
		6.3.1 Order of ECOG PS at Baseline in list of Analysis Variables amended to match order of presentation in the corresponding summary table.
		6.4.2 Study Day 1 changed to TAK-103 Infusion for consistency.
		6.5.1.4 Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Analytical Methods.
		6.6.1.1 Text added to include Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events in the Overview of Treatment-Emergent Adverse Events summary in the Analytical Methods. Text added to include Grade 3 or higher Study Procedure-Related Treatment-Emergent Adverse Events in the Overview of Treatment-Emergent Adverse Events summary in the Analytical Methods. Text added to include Product/Conditioning Chemotherapy/Study Procedure-Related Serious Treatment-Emergent Adverse Events in the Overview of Treatment-Emergent Adverse Events summary in the Analytical Methods.

		<p>Text added to include Relationship of serious Treatment-Emergent Adverse Events to Conditioning Chemotherapy in the Overview of Treatment-Emergent Adverse Events summary in the Analytical Methods.</p> <p>Text added to include Relationship of serious Treatment-Emergent Adverse Events to Study Procedure in the Overview of Treatment-Emergent Adverse Events summary in the Analytical Methods.</p> <p>Summary numbers for Number of Subjects updated accordingly.</p>
	6.6.1.2	DLT-evaluable Set corrected to DLT Analysis Set for consistency with 5.2.
	6.6.1.3	<p>Text added to include Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events in the list of summaries in the Analytical Methods.</p> <p>Summary numbers for Number of Subjects updated accordingly.</p>
	6.6.1.4	<p>New section - Overview of Conditioning Chemotherapy-Emergent Adverse Events text added.</p> <p>Subsequent sections renumbered.</p>
	6.6.1.6	<p>New section - Overview of Pretreatment Events text added.</p> <p>Subsequent sections renumbered.</p>
	6.6.3.1	Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit.
	6.6.3.2	Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit.
	6.6.4	<p>Categories section removed since Toxicity Grade is not assessed for Vital Signs.</p> <p>Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit.</p> <p>Summary of Shifts in Vital Signs Parameters removed as it is not relevant.</p>
	6.6.6.3	Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit.
	6.6.7	Text updated to specify Total CAR-T Cell Number of TAK-103 Administered rather than Administered Dose.

		<p>Text added to include Total Amount of Conditioning Chemotherapy Converted to BSA in the list of Analysis Variables.</p> <p>Text added to clarify Summary of Total CAR-T Cell Number of TAK-103 Administered in the list of Analytical Methods.</p> <p>Text added to include Summary of Total Amount of Conditioning Chemotherapy Converted to BSA in the list of Analytical Methods.</p> <p>6.7 Text added to specify the list of CK/Pharmacodynamic parameters that will be presented.</p> <p>6.7.1 Section deleted.</p> <p>6.8.1 Analysis Set changed to Immunogenicity-evaluable Analysis Set rather than the Safety Analysis Set.</p> <p>Table 9.a Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 19, 25, 31, 37.</p> <p>Table 9.b Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 37.</p> <p>Table 9.c Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 13, 37.</p> <p>Table 9.d Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 19, 25, 31, 37.</p> <p>Table 9.e Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 19, 25, 31, 37.</p> <p>Table 9.f Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table for Day 29.</p>
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		<p>Table 9.g Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Interval amended for Months 4, 7, 13, 19, 25, 31, 37.</p> <p>Table 9.h Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table for Day 4. Time Intervals added to the table for Day 8.</p> <p>Table 9.i Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 19, 25, 31, 37.</p> <p>Table 9.j Pre-Conditioning Chemotherapy corrected to Conditioning Chemotherapy in the Visit column. Time Intervals added to the table. Time Interval amended for Months 7, 10, 13, 19, 25, 31, 37.</p> <p>9.2.3 New section - Conventions for Handling of Missing/Partial Dates text added. Subsequent sections renumbered.</p>
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ABBREVIATIONS

ACT	adoptive cell transfer
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
BLQ	below the limit of quantification
BSA	body surface area
BOIN	Bayesian Optimal Interval
CA125	Cancer Antigen 125
CA19-9	Cancer Antigen 19-9
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T cell
CARTOX	CAR-T-cell-therapy-associated TOXicity
CCL19	chemokine (C-C motif) ligand 19
CEA	Carcino Embryonic Antigen
CK	cellular kinetics
C _{last}	last observed quantifiable concentration in peripheral blood (CAR copies/μg of gDNA or CAR+ cells/μL)
C _{max}	maximum (peak) observed in peripheral blood product concentration after single dose administration (CAR copies/μg of gDNA or CAR+ cells/μL)
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	coefficient of variation
DC	dendritic cell
DCR	disease control rate
ddPCR	droplet digital polymerase chain reaction
DLT	dose-limiting toxicity
DOR	duration of response
DW-MRI	diffusion-weighted magnetic resonance imaging
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
ECD	extracellular domain
eCRF	electronic case report form
EMA	European Medicines Agency
EOPF	end of primary follow-up
EOS	end of study
EPI	echo planar imaging
FCM	flow cytometry
FDA	Food and Drug Administration [United States]
FDG-PET	fluorodeoxyglucose-position emission tomography
FFPE	formalin-fixed, paraffin-embedded
FIH	first in human
GCP	Good Clinical Practice
GvHD	graft versus host disease
gDNA	genomic DNA
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HEK	human embryonic kidney (cell line)
HepG2	human hepatocellular carcinoma (cell line)
HepG2-Red-FLuc	luciferase-expressing HCC cell line derived from HepG2
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune-confirmed progressive disease
iCR	immune complete response
IEC	independent ethics committee
IFNg	interferon gamma
IHC	immunohistochemistry
IL	interleukin
I/O	immuno-oncology
iPR	immune partial response
iRECIST	immune Response Evaluation Criteria in Solid Tumors (a modified Response Criteria in Solid Tumors Version 1.1 for immune-based therapeutics)
IRB	institutional review board

iSD	immune stable disease
iUPD	immune-unconfirmed progressive disease
IV	intravenous(ly)
kDa	kilodalton
LAM-PCR	linear amplification-mediated polymerase chain reaction
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MPF	megakaryocyte potentiating factor
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MTV	mean tumor volume
NCI	National Cancer Institute
NK	natural killer cell
NLNT	new lesion-non-target
NLT	new lesions-target
NSCLC	non-small-cell lung cancer
NSG	NOD SCID Gamma
ORR	overall response rate
OS	overall survival
PMPA	plasma membrane protein array
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffer saline
PET	positron emission tomography
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]
PT	prothrombin time
PR	partial response
PRIME CAR-T	proliferation-inducing and migration-enhancing CAR-T
RCR	replication competent retrovirus
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
rm	recombinant mouse
RNAseq	ribonucleic acid sequencing
RP2D	recommended phase 2 dose
SAE	serious adverse event
SC	subcutaneously
scFv	single-chain variable fragment

SD	stable disease
SMRP	soluble mesothelin-related peptides
SOC	standard of care
SOE	schedule of events
SpO ₂	percutaneous oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TF	total flux
TGI	tumor growth inhibition
t _{last}	time of last observed quantifiable concentration in peripheral blood (days)
TLS	tumor lysis syndrome
TMB	tumor mutational burden
t _{max}	time of first occurrence of maximum observed CAR-T cell concentration (C _{max}) in peripheral blood
TTP	time to progression
TV	tumor volume
ULN	upper limit of the normal range
UPENN	University of Pennsylvania
US	United States
UTD	untransduced
WBC	white blood cell
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

- *To evaluate the safety and tolerability of TAK-103.*
- *To determine the recommended phase 2 dose (RP2D) of TAK-103.*

1.1.2 Secondary Objectives

- *To evaluate the antitumor activity of TAK-103.*
- *To characterize the cellular kinetics of TAK-103.*
- *To determine the number and percent of cases with replication competent retrovirus (RCR)-positive test results.*

1.1.3 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

1.2 Endpoints

1.2.1 Primary Endpoints

- *Incidence of dose limiting toxicities (DLTs).*
- *Incidence of treatment-emergent adverse events (TEAEs).*
- *Incidence of AEs of clinical interest including severe immune effector cell-associated neurotoxicity syndrome (ICANS), cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and tumor lysis syndrome (TLS).*

1.2.2 Secondary Endpoints

- *Overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), and progression-free survival (PFS) as assessed by the investigator*

- Overall survival (OS).
- Cellular kinetics (CK)-related parameters (C_{max} [maximum (peak) observed in peripheral blood drug concentration after single dose administration], t_{max} [time of first occurrence of maximum observed peripheral blood concentration], C_{last} [last observed quantifiable concentration in peripheral blood], t_{last} [persistence: time of last observed quantifiable concentration in peripheral blood (days)]; AUC [area under the blood concentration-time curve]).
- Number and percentage of cases with RCR-positive test results.

- [REDACTED]
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1.3 Estimand

Not Applicable

2.0 STUDY DESIGN

Study TAK-103-1001 is an open-label, non-randomized, phase 1, first in human (FIH) study to evaluate the safety and tolerability of TAK-103 administered intravenously (IV) in patients with mesothelin-expressing advanced or metastatic solid tumors with no standard therapeutic alternative with established clinical benefit. Ovarian cancer and mesothelioma are the high priority target population for TAK-103, given the prevalence of high mesothelin expression and prior clinical evidence of mesothelin-targeting autologous CAR-T. Non-small-cell lung cancer (NSCLC) and gastric cancer patients are also hypothesized to benefit from TAK-103 due to reported mesothelin expression and clinical activity with immune checkpoint inhibitors (immune-sensitive).

The patient population will consist of adults with a diagnosis of solid tumors with confirmed mesothelin-expression determined on the tumor by IHC and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients must also have radiographically measurable disease as defined by RECIST 1.1. Eligibility must be confirmed, reviewed/reconfirmed before leukapheresis procedures and conditioning chemotherapy (or TAK-103 administration when conditioning chemotherapy is not administered), respectively.

Up to 21 DLT evaluable patients will be treated with TAK-103. Patients will be enrolled in the study and treated with TAK-103 starting with Cohort (-2) and sequentially to the next dosing

cohort up to Cohort 3 in accordance with dose escalation schema. Dose levels between planned cohorts may also be tested following discussion between the sponsor and the investigators.

- Cohort (-2): 1×10^6 CAR (+) cells/body [starting dose at resumption].
- Cohort (-1): 0.3×10^7 CAR (+) cells/body
- Cohort 1: 1×10^7 CAR (+) cells/body [starting dose].
- Cohort 2: 1×10^8 CAR (+) cells/body.
- Cohort 3: 5×10^8 CAR (+) cells/body.

Each patient will receive a single IV infusion of TAK-103 in this study.

Conditioning chemotherapy is started before TAK-103 infusion so that TAK-103 cells will be administered approximately 3 days after completion of the conditioning chemotherapy. TAK-103 infusion after conditioning chemotherapy may be delayed for up to 14 days based on medical judgement by the investigators. The regimen for conditioning chemotherapy consists of fludarabine (30 mg/m^2 IV daily for 3 doses on Days -5, -4 and -3) and cyclophosphamide (500 mg/m^2 IV daily for 3 doses starting with the first dose of fludarabine).

Cohorts where conditioning chemotherapy is not administered may be tested. For instance, the use of conditioning chemotherapy is concerning potential association with the development of AEs. If de-escalation of TAK-103 is necessary due to DLTs, TAK-103 infusion without conditioning chemotherapy may be examined to confirm safety of TAK-103. As another potential scenario, TAK-103 is armored CAR-T, where there is a possibility of remarkable efficacy without conditioning chemotherapy. TAK-103 infusion without conditioning chemotherapy may be investigated once significant efficacy of TAK-103 infusion with conditioning chemotherapy is confirmed.

TAK-103 will be shipped to the clinical site in a proper container which can maintain and control cryopreserved condition. TAK-103 is to be administered on Day 1 at approximately 5 mL/min within 60 minutes after being thawed. The investigator should complete the administration as soon as possible to maintain the quality of the study product.

During the Pretreatment phase, bridging therapy may be performed with any approved regimen for the subject's malignancy. [REDACTED]

[REDACTED] Patients cannot use medications including systemic steroids and anticancer treatments that can impact the product function or confound interpretation of immunologic correlates during the Treatment and Primary Follow-up phase and Secondary Follow-up phase unless there is medical need.

Dose escalation will be guided by the Bayesian Optimal Interval (BOIN) design. The BOIN design is based on the observed toxicity probabilities for each dose level. Dose escalation/de-escalation decisions will be determined within the recommended dose by BOIN, taking into account safety, efficacy, and CK, and be made jointly by the sponsor and the investigator at meetings, including the cohort management meetings. Additional emerging translational data (eg, soluble mesothelin, CA125) may also be used, when feasible, to aid

decision-making of dosing additional patients at a given dose level. RP2D will be determined based on aggregated observations of safety, efficacy, CK, and biomarker assessments at each dose level.

In any Cohorts, infusion of TAK-103 of every patient will be separated by 28 (or more) days. Dose cohorts will be separated by a minimum of 28 days (from the last TAK-103 infusion in the precedent cohort to the first TAK-103 infusion in the subsequent cohort).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. CRS and ICANS will be evaluated according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus. The management of CRS and ICANS will follow the management procedures of the sites with CRS/ICNS management manual for this clinical trial provided by the sponsor. For management of HLH and MAS, CARTOX (CAR-T-cell-therapy-associated TOXicity) recommendations will be used in principal. DLT will be defined as Grade 3 or higher toxicities that are considered by the investigator to be at least possibly related to therapy with TAK-103 during the 28 days immediately following TAK-103 infusion. Events which the investigator identifies as clinically significant may be considered as an additional DLT upon discussion with the sponsor.

The study consists of the Prescreening, Screening, Pretreatment, Treatment and Primary Follow-up, and Secondary Follow-up phases.

- The Prescreening phase may begin on the date the patient signs the institutional review board/independent ethics committee (IRB/IEC)-approved informed consent form (ICF) (Prescreening ICF) for the assessment of mesothelin expression in tumor cells. The patient is provided with a study-specific patient number on the date of Prescreening ICF.*
- The Screening phase starts with the date when one of procedures in the Screening phase take place. If the patient's mesothelin expression status is already analyzed with the patient's archived tumor tissue sample using Takeda validated assay and the patient participates in the study from the Screening phase, a study-specific patient number is provided on the date of Main ICF. The Screening phase includes confirmation of eligibility and enrollment into the study, and ends with the start of leukapheresis procedures.*
- The Pretreatment phase is defined as the period from the start of leukapheresis procedures through the completion of conditioning chemotherapy until the start of TAK-103 infusion. During the Pretreatment phase, leukapheresis, bridging therapy, and conditioning chemotherapy will be performed.*
- The Treatment and Primary Follow-up phase begins with TAK-103 administration and continues up to Month 13.*
- Secondary follow-up phase begins with the end of the Treatment and Primary Follow-up period and continues up to Month 37.*

In the Pretreatment phase, the Treatment and Primary Follow-up and Secondary Follow-up phases, patients may complete study participation due to death, consent withdrawal, or other predefined situations.

Patients must be followed according to the visit schedule to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. Patients may voluntarily withdraw from the Treatment and Primary Follow-up phase or be dropped from it at the discretion of the investigator at any time. It is anticipated that patients may leave the Primary Follow-up and move to Secondary Follow-up due to reasons including:

- *Disease progression*
- *Patient voluntary withdrawal from the Primary Follow-up*

Patients who discontinue the Treatment and Primary Follow-up phase before Month 13 will continue to be followed in the Secondary Follow-up phase in order to collect safety data requested from health authority (eg, protocol defined AEs) up to 3 years after TAK-103 infusion.

The first visit in the Secondary Follow-up phase is determined according to the time when the patient discontinued in the Treatment and Primary Follow-up phase. For example, if the patient discontinues from the Treatment and Primary Follow-up phase at Month 7, the first visit in the Secondary Follow-up phase will be Month 10. Secondary Follow-up phase is set to evaluate long-term toxicity which is required by health authority. It is not considered to be a protocol deviation if patients refuse non-safety assessment (eg, disease assessment, sampling for biomarker, CK, or pharmacodynamic assessment) during Secondary Follow-up phase.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable

3.2 Statistical Decision Rules

Not Applicable

3.3 Multiplicity Adjustment

Not Applicable

4.0 SAMPLE-SIZE DETERMINATION

It is anticipated that up to 21 DLT evaluable patients will be enrolled in this study. The study will use BOIN design to inform dose escalation/de-escalation decisions, taking into account safety other than DLTs, efficacy, CK, and biomarker assessments.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

Patients who have received any dose of TAK-103. This set will primarily be used for safety analyses and for some efficacy analyses.

5.2 DLT Analysis Set

Patients who have received any predetermined dose of TAK-103 and completed the assessment for DLT evaluation or experienced a DLT during the first 28 days following TAK-103 infusion. The DLT analysis set will be used to determine the MTD.

5.3 CK Analysis Set

Patients who have received any dose of TAK-103 and have at least 1 CK parameter estimated will be used for CK analysis.

5.4 Response-evaluable Analysis Set

Patients who have received any dose of TAK-103, have had measurable disease at baseline and at least 1 posttreatment evaluation, will be used for analyses of response.

5.5 Pharmacodynamics Analysis Set

Patients from the safety analysis set who have baseline and at least 1 postbaseline sample assessment.

5.6 Immunogenicity-evaluable Analysis Set

Patients from the safety analysis set who have baseline and at least 1 postbaseline immunogenicity assessment.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event: An adverse event which newly occurs or worsens after administration of TAK-103
- Conditioning chemotherapy-emergent adverse event: An adverse event which newly occurs or worsens after conditioning chemotherapy and before administration of TAK-103
- Pretreatment event (PTE): An adverse event which occurs before conditioning therapy (if conditioning chemotherapy was performed) or before administration of TAK-103 (if conditioning chemotherapy was NOT performed)

- Treatment-emergent adverse events resulting in death: An adverse event of which outcome is fatal or toxicity grade is Grade 5
- Treatment-emergent ICANS/CRS sign and symptom: A sign/symptom in ICANS or CRS which occurs after administration of TAK-103
- Subjects who signed the informed consent form are defined as those who signed at least one of pre-screening consent and main informed consent. Date of the subject signed informed consent form is defined as the date of pre-screening consent or main informed consent obtained, whichever is earlier.
- Subjects who enter the pretreatment phase are defined as those who start leukapheresis procedures.
- Subjects who enter the treatment and primary follow-up phase are defined as those who start TAK-103 infusion.
- For subjects who start TAK-103 infusion, if the action taken with study treatment is Drug Withdrawn, they will be treated as “Discontinued TAK-103 Infusion”. Otherwise, they will be treated as “Completed TAK-103 Infusion”.
- Time since initial diagnosis is defined as the time from the date of initial diagnosis to the date of TAK-103 infusion. Time since initial diagnosis will be expressed in months, i.e. Time since initial diagnosis = (date of TAK-103 infusion – date of initial diagnosis) / 30.4375. (If month of diagnosis is missing, month will be replaced with January. If day of diagnosis is missing, day will be replaced with 1st.)
- Time since leukapheresis is defined as the time from the date of leukapheresis to the date of TAK-103 infusion. Time since leukapheresis will be expressed in day, i.e. Time since leukapheresis = (date of TAK-103 infusion – date of leukapheresis).
- QTcF and QTcB intervals will be calculated by the following formula:
$$\text{QTcF interval (msec)} = \text{QT interval (msec)} / (\text{RR interval (sec)})^{0.33} \text{ (rounded to the nearest whole number)}$$
$$\text{QTcB interval (msec)} = \text{QT interval (msec)} / (\text{RR interval (sec)})^{0.5} \text{ (rounded to the nearest whole number)}$$
- Mesothelin H-score will be calculated by the following formula and will range from 0 to 300.
$$\text{H-score} = (\% \text{ of } 1) * 1 + (\% \text{ of } 2) * 2 + (\% \text{ of } 3) * 3 \text{ (rounded to the nearest whole number)}$$
- Mesothelin Total Positive Staining (TPS) Score (%) will be calculated by the following formula and will range from 0 to 100.
$$\text{TPS score} = (\% \text{ of } 1) + (\% \text{ of } 2) + (\% \text{ of } 3) \text{ (rounded to the nearest whole number)}$$
- Total CAR-T cell number of TAK-103 administered will be calculated by multiplying the product parameter provided by TakaraBio by dosing information from EDC using the following formula:

Total CAR-T cell number of TAK-103 administered (cells/body) = Actual dose (cells/bag) *
Dose (mL) / 50 (mL)

- Total amount of conditioning chemotherapy converted to BSA will be calculated by the following formula:

Total amount of conditioning chemotherapy (mg/m²) = Dose (mg) / BSA (m²)

where BSA will be calculated using DeBois formula: BSA = (Weight (kg) at Conditioning Chemotherapy)^{0.425} * Height (cm)^{0.725} * 0.007184

6.1.1 Handling of Treatment Misallocations

Not Applicable.

6.1.2 Analysis Approach for Continuous Variables

All continuous variables will be summarized with descriptive statistics (number of subjects with non-missing values, mean, standard deviation, maximum, minimum, and quartiles) unless stated otherwise in the section specific to an endpoint.

6.1.3 Analysis Approach for Binary Variables

All binary variables will be presented with the number and percent per category unless stated otherwise in the section specific to an endpoint. Missing test results will not be used for the analyses unless specified.

6.1.4 Analysis Approach for Time-to-Event Variables

All time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as the survival probability at specified timepoints.

6.2 Disposition of Subjects

6.2.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date of First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

6.2.2 Screen Failures

Analysis Set:

All Subjects Who Signed the Informed Consent Form but Not Enter the Pretreatment Period

Analysis Variables:

Age (years)	[20<= - <65, 65<= - <=Max]
Gender	[Male, Female]
Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported]
Race (Asian)	[Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Not Reported]
Ethnicity	[Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown]
Anatomic Stage	[I, IA, IB, IC, ID, II, IIA, IIB, IIC, IID, III, IIIA, IIIB, IIIC, IIID, IV, IVA, IVB, IVC, IVD, Other, Not Available]
Time Since Initial Diagnosis	
Diagnosis	[Malignant pleural mesothelioma, Ovarian cancer, Malignant peritoneal mesothelioma, Gastric Cancer, Non-Small Cell Lung Cancer, Other]
Mesothelin TPS Score (%)	
Mesothelin H-Score	

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.2.3 Subject Eligibility

6.2.3.1 Subject Eligibility for Entrance into the Screening Phase

Analysis Set:

All Subjects Who Signed the Pre-screening Informed Consent Form

Analysis Variables:

Eligibility Status [Eligible for Entrance into the Screening Phase, Not Eligible for Entrance into the Screening Phase]

Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Screening Phase

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

6.2.3.2 Subject Eligibility for Entrance into the Pretreatment Phase

Analysis Set:

All Subjects Who Signed the Main Informed Consent Form

Analysis Variables:

Eligibility Status [Eligible for Entrance into the Pretreatment Phase, Not Eligible for Entrance into the Pretreatment Phase]

Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Pretreatment Phase

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

6.2.4 Number of Subjects Who Entered the Pretreatment Phase by Site

Analysis Set:

All Subjects Who Entered the Pretreatment Phase

All Subjects Who Entered the Treatment and Primary Follow-up Phase

Analysis Variables:

Status of Entrance into the Pretreatment Phase [Entered]

Status of Entrance into the Treatment and Primary Follow-up Phase [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Pretreatment Phase by Site

Frequency distribution will be provided for each stratum.

(2) Number of Subjects Who Entered the Treatment and Primary Follow-up Phase by Site

Frequency distribution will be provided for each stratum.

6.2.5 Disposition of Subjects

6.2.5.1 *Disposition of subjects who entered the Pretreatment Phase*

Analysis Set:

All Subjects Who Entered the Pretreatment Phase

Analysis Variables:

Completion Status of Pretreatment Phase

[Ongoing, Entered Treatment and Primary Follow-up Phase, Discontinued Without Receiving TAK-103 Infusion]

Reason for Not Entering Treatment and Primary Follow-up Phase

[Adverse Event, Death, Failure to Meet Continuation Criteria, Lost to Follow-up, Pregnancy, Progressive Disease, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study product will be used as the denominator.

6.2.5.2 *Disposition of subjects who entered the Treatment and Primary Follow-up Phase*

Analysis Set:

All Subjects Who Entered the Treatment and Primary Follow-up Phase

Analysis Variables:

Completion Status of Study Treatment

[Completed TAK-103 infusion, Discontinued TAK-103 infusion]

Completion Status of Treatment and Primary Follow-up Phase

[Ongoing, Completed, Discontinued Treatment and Primary Follow-up Phase]

Reason for Discontinuation of Treatment and Primary Follow-up Phase

[Adverse Event, Death, Failure to Meet Continuation Criteria, Lost to Follow-up, Pregnancy, Progressive Disease, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.5.3 *Disposition of subjects who entered the Secondary Follow-up Phase*

Analysis Set:

All Subjects Who Entered the Secondary Follow-up Phase

Analysis Variables:

Completion Status of Secondary Follow-up Phase

[Ongoing, Completed, Discontinued Secondary Follow-up Phase]

Reason for Discontinuation of Secondary Follow-up Phase

[Adverse Event, Death, Failure to Meet Continuation Criteria, Lost to Follow-up, Pregnancy, Progressive Disease, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.6 Protocol Deviations and Analysis Sets

6.2.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Pretreatment Phase

Analysis Variables:

Significant Protocol Deviation

[Categories are based on the specifications in Protocol Deviation Management Plan]

Analytical Methods:

(1) Protocol Deviations

Frequency distribution of subjects with significant protocol deviations, as identified by the study team as being major or critical, will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

6.2.6.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment and Primary Follow-up Phase

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Safety Analysis Set	[Included]
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DLT Analysis Set	[Included]
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CK Analysis Set	[Included]
-----------------	------------

Response-evaluable Analysis Set	[Included]
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Pharmacodynamic Analysis Set	[Included]
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Immunogenicity-evaluable Analysis Set	[Included]
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Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided by dose cohort and overall. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Other Baseline Characteristics

Analysis Set:

All Subjects Who Entered the Treatment and Primary Follow-up Phase

Analysis Variables:

Age (years)	[20<= - <65, 65<= - <=Max]
Gender	[Male, Female]
Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported]
Race (Asian)	[Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Not Reported]
Ethnicity	[Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown]
Height (cm)	
Weight (kg) at Baseline	[Min<= - <60, 60<= - <=Max]
ECOG PS at Baseline	[0, 1]
Diagnosis	[Malignant pleural mesothelioma, Ovarian cancer, Malignant peritoneal mesothelioma, Gastric Cancer, Non-Small Cell Lung Cancer, Other]
Time Since Initial Diagnosis (months)	
Anatomic Stage	[I, IA, IB, IC, ID, II, IIA, IIB, IIC, IID, III, IIIA, IIIB, IIIC, IIID, IV, IVA, IVB, IVC, IVD, Other, Not Available]
Prior Anti-Cancer Therapy	[Yes, No]
Number of Regimen	[1, 2, 3, 4, 5 or more]

Prior Radiotherapy	[Yes, No]
Prior Surgery/Procedure	[Yes, No]
Conditioning Chemotherapy	[Yes, No]
Bridging Anti-Cancer Therapy	[Yes, No]
Bridging Radiotherapy	[Yes, No]
Bridging Surgery/Procedure	[Yes, No]
Time Since Leukapheresis	
Mesothelin TPS Score (%)	
Mesothelin H-Score	
HIV at Screening	[Positive, Negative]
HTLV at Screening	[Positive, Negative]
HBsAg at Screening	[Positive, Negative]
HBsAb at Screening	[Positive, Negative]
HBcAb at Screening	[Positive, Negative]
HCVAb at Screening	[Positive, Negative]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by dose cohort and overall. Any analyses variables will be summarized for all subjects who entered the treatment and primary follow-up phase.

6.3.2 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

- (1) Medical History by System Organ Class and Preferred Term
- (2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided by dose cohort and overall. MedDRA dictionary will be used for coding. Summaries will be provided using System Organ Class and Preferred Term, where System Organ Class will be sorted alphabetically and Preferred Term will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a System Organ Class will be counted only once in that System Organ Class. A subject with multiple occurrences of medical history or concurrent medical condition within a Preferred Term will be counted only once in that Preferred Term.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior Anticancer Therapy

Analytical Methods:

- (1) Prior Anticancer Therapy by Preferred Medication Name

Frequency distributions will be provided by dose cohort and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.4.2 Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Concomitant Medications

Analytical Methods:

- (1) Concomitant Medications That Started and Stopped Prior to TAK-103 Infusion by Preferred Medication Name.

- (2) Concomitant Medications That Started Prior to and Were Ongoing at TAK-103 Infusion as well as Those That Started On or After TAK-103 Infusion by Preferred Medication Name

Frequency distributions will be provided by dose cohort and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.5 Efficacy Analysis

6.5.1 Secondary Endpoints Analysis

6.5.1.1 Derivation of Endpoints

- The best overall response (BOR) is the best timepoint response per RECIST 1.1 recorded from TAK-103 infusion until the end of primary follow-up disease assessment, the last disease assessment before a new anticancer treatment has started or the first disease progression, whichever occurs first and is defined as 'better' in the order of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). When SD is believed to be best response, it must be maintained for at least 24 days (around 4 weeks) after the date of TAK-103 administration. A patient who is evaluated SD at less than 24 days (around 4 weeks) after the date of TAK-103 administration (does not meet the SD criteria) and subsequently lost to follow-up would be treated as NE.
- The immune best overall response (iBOR) is the best timepoint response per iRECIST recorded from TAK-103 infusion until the end of primary follow-up disease assessment, the last disease assessment before a new anticancer treatment has started or the first disease progression, whichever occurs first and is defined as 'better' in the order of immune complete response (iCR), immune partial response (iPR), immune stable disease (iSD), immune confirmed progressive disease (iCPD), immune unconfirmed progressive disease (iUPD), and NE. When iSD is believed to be best response, it must be maintained for at least 24 days (around 4 weeks) after the date of TAK-103 administration. A patient who is evaluated iSD at less than 24 days (around 4 weeks) after the date of TAK-103 administration (does not meet the iSD criteria) and subsequently lost to follow-up would be treated as NE.
- PD date is defined as the date of the first documentation of PD per RECIST 1.1.
- iPD date is defined as the date of progression per iRECIST. Further details are given in Appendix.
- ORR is defined as the proportion of patients whose BOR is CR or PR in response-evaluable analysis set.
- iORR is defined as the proportion of patients whose iBOR is iCR or iPR in response-evaluable analysis set.

- DCR is defined as the proportion of patients whose BOR is CR, PR, or SD in response-evaluable analysis set.
- iDCR is defined as the proportion of patients whose iBOR is iCR, iPR, or iSD in response-evaluable analysis set.
- DOR is defined as the time from the date of first documentation of a PR or better to the PD date or date of death from any cause, whichever occurs first, for responders (BOR is PR or better). The DOR will be expressed in months, i.e. $DOR = (\text{earliest of PD date or Death} - \text{earliest of date of PR or better} + 1) / 30.4375$. Censoring rules for the analysis of DOR will be the same as those for PFS.
- iDOR is defined as the time from the date of first documentation of a iPR or better to the iPD date or date of death from any cause, whichever occurs first, for immune responders (iBOR is iPR or better). The iDOR will be expressed in months, i.e. $iDOR = (\text{earliest of iPD date or Death} - \text{earliest of date of iPR or better} + 1) / 30.4375$. Censoring rules for the analysis of iDOR will be the same as those for iPFS.
- TTP is defined as the time from the TAK-103 infusion date to the PD date. TTP will be expressed in months, i.e., $TTP = (\text{PD date} - \text{TAK-103 infusion date} + 1) / 30.4375$. Censoring rules for the analysis of TTP will be the same as those for PFS, except that death without progression will be censored at the death date.
- iTTP is defined as the time from the TAK-103 infusion date to the iPD date. iTTP will be expressed in months, i.e., $iTTP = (\text{iPD date} - \text{TAK-103 infusion date} + 1) / 30.4375$. Censoring rules for the analysis of iTTP will be the same as those for iPFS, except that death without progression will be censored at the death date.
- PFS is defined as the time from the TAK-103 infusion date to the PD date or death from any cause, whichever occurs first. PFS will be expressed in months, i.e., $PFS = (\text{earliest of PD date or Death} - \text{TAK-103 infusion date} + 1) / 30.4375$.
General censoring rules for the analysis of PFS will be as follows:
 - Patients who have no adequate baseline and/or post-baseline radiological assessments will be censored at TAK-103 infusion date, except that death occurred within 67 days after TAK-103 infusion will be a PFS event at death date.
 - Patients known to be alive and known not to have started new (non-protocol) anti-cancer treatment, who are progression-free, and who have a baseline and at least 1 post-dosing radiological assessment, are censored at the date of the last radiological assessment that verified lack of PD.
 - Patients starting new anti-cancer treatment prior to progression or death are censored at the date of last radiological assessment documenting no progression prior to the new treatment.
 - Documentation of progression or death after an unacceptably long interval (2 consecutive missed or indeterminate objective response assessments) since the last

radiological assessment will be censored at the date of last radiological assessment documenting no progression.

- iPFS is defined as the time from the TAK-103 infusion date to the iPD date or death from any cause, whichever occurs first. iPFS will be expressed in months, i.e., $iPFS = ((\text{earliest of iPD date or Death}) - \text{TAK-103 infusion date} + 1) / 30.4375$.
General censoring rules for the analysis of iPFS will be similar to PFS, except that iPD date instead of PD date will be used.
- OS: The time from the TAK-103 infusion date to the date of death from any cause. Patients known to be alive will be censored at the last known survival follow-up date. OS will be expressed in months, i.e., $OS = (\text{Death date} - \text{TAK-103 infusion date} + 1) / 30.4375$.

6.5.1.2 Overall response per RECIST 1.1

Analysis Set:

Response-evaluable Analysis Set

Analysis Variables:

BOR [CR, PR, SD, PD, NE]

ORR

DCR

Overall Response per RECIST 1.1 [CR, PR, SD, PD, NE]

Analytical Methods:

(1) Summary of BOR, ORR and DCR

For BOR, frequency distributions will be provided by dose cohort and overall.

For ORR and DCR, point estimate and the 2-sided 95% exact CI will be provided by dose cohort and overall.

(2) Swimmer plot

A swimmer plot of overall response per RECIST 1.1 by subject will be provided.

6.5.1.3 Overall response per iRECIST

Analysis Set:

Response-evaluable Analysis Set

Analysis Variables:

iBOR [iCR, iPR, iSD, iCPD, iUPD, NE]

iORR

iDCR

Overall Response per iRECIST [iCR, iPR, iSD, iCPD, iUPD, NE]

Analytical Methods:

(1) Summary of iBOR, iORR and iDCR

For iBOR, frequency distributions will be provided by dose cohort and overall.

For iORR and iDCR, point estimate and the 2-sided 95% exact CI will be provided by dose cohort and overall.

(2) Swimmer plot

A swimmer plot of overall response per iRECIST by subject will be provided.

6.5.1.4 Percent Change in Target Lesion

Analysis Set:

Response-evaluable Analysis Set

Analysis Variables:

Best percent change in target lesion per RECIST 1.1

Percent change in target lesion per RECIST 1.1

Analytical Methods:

(1) Waterfall plot

A waterfall plot of best percent change from baseline (Conditioning Chemotherapy visit) in the sum of target lesion diameters will be presented. The best percent change is defined as the biggest decrease, or smallest increase if no decrease.

Only the target lesion diameters measured on or prior to the earlier of the date of PFS event or date of censoring for PFS per RECIST 1.1 will be used.

(2) Spider plot

A spider plot of percent change from baseline (Conditioning Chemotherapy visit) in the sum of target lesion diameters will be presented.

Only the target lesion diameters measured on or prior to the earlier of the date of PFS event or date of censoring for PFS per RECIST 1.1 will be used.

6.5.1.5 DOR

Analysis Set:

Response-evaluable Analysis Set

Analysis Variables:

DOR

iDOR

Analytical Methods:

For DOR, the following analyses will be performed by dose cohort and overall.

Breakdown of the number of subjects who were censored and who experienced an event will be summarized. Quartiles of DOR and the two-sided 95% confidence intervals will be estimated using the Kaplan-Meier method. Kaplan-Meier estimate of DOR proportion at specified points will also be provided. The Kaplan-Meier plot of DOR will be presented.

For iDOR, the same analyses as those for DOR will be conducted.

6.5.1.6 TTP

Analysis Set:

Safety Analysis Set

Analysis Variables:

TTP

iTTP

Analytical Methods:

For TTP and iTTP, the same analyses as those for DOR will be conducted using the Safety Analysis Set.

6.5.1.7 PFS

Analysis Set:

Safety Analysis Set

Analysis Variables:

PFS

iPFS

Analytical Methods:

For PFS and iPFS, the same analyses as those for DOR will be conducted using the Safety Analysis Set.

6.5.1.8 OS

Analysis Set:

Safety Analysis Set

Analysis Variables:

OS

Analytical Methods:

For OS, the same analyses as those for DOR will be conducted using the Safety Analysis Set.

6.6 Safety Analysis

6.6.1 Adverse Events

6.6.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Product [Related, Not Related]

Relationship to Conditioning Chemotherapy [Related, Not Related]

Relationship to Study Procedure [Related, Not Related]

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided for each dose cohort and overall.

(1) Overview of Treatment-Emergent Adverse Events

- 1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 2) Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 3) Relationship of Treatment-Emergent Adverse Events to Study Product (number of events, number and percentage of subjects)
- 4) Relationship of Treatment-Emergent Adverse Events to Conditioning Chemotherapy (number of events, number and percentage of subjects)
- 5) Relationship of Treatment-Emergent Adverse Events to Study Procedure (number of events, number and percentage of subjects)

- 6) Grade 3 or higher Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 7) Grade 3 or higher Product-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 8) Grade 3 or higher Conditioning Chemotherapy-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 9) Grade 3 or higher Study Procedure-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 10) Toxicity Grade of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 11) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 12) Product/Conditioning Chemotherapy/Study Procedure-Related Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
- 13) Relationship of serious Treatment-Emergent Adverse Events to Study Product (number of events, number and percentage of subjects)
- 14) Relationship of serious Treatment-Emergent Adverse Events to Conditioning Chemotherapy (number of events, number and percentage of subjects)
- 15) Relationship of serious Treatment-Emergent Adverse Events to Study Procedure (number of events, number and percentage of subjects)
- 16) Treatment-Emergent Adverse Events Leading to Dose Rate Reduced (number of events, number and percentage of subjects).
- 17) Product-Related Treatment-Emergent Adverse Events Leading to Dose Rate Reduced (number of events, number and percentage of subjects).
- 18) Treatment-Emergent Adverse Events Leading to Drug Withdrawn (number of events, number and percentage of subjects).
- 19) Product-Related Treatment-Emergent Adverse Events Leading to Drug Withdrawn (number of events, number and percentage of subjects).
- 20) Treatment-Emergent Adverse Events Leading to Dose Infusion Interrupted (number of events, number and percentage of subjects).
- 21) Product-Related Treatment-Emergent Adverse Events Leading to Dose Infusion Interrupted (number of events, number and percentage of subjects).
- 22) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

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Number of subjects

- Summaries for 3), 4), 5), 13), 14) and 15)

A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 10)

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 3), 4), 5), 10), 13), 14) and 15)

A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

6.6.1.2 *Frequency of Subjects with DLTs during the first 28 days following TAK-103 infusion*

Analysis Set:

DLT Analysis Set

Analysis Variables:

DLTs during the first 28 days

Analysis Method(s):

DLT will be summarized by system organ class and preferred term for each dose cohort and overall.

6.6.1.3 *Displays of Treatment-Emergent Adverse events*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided using frequency distribution by dose cohort and overall.

TEAEs will be coded using the MedDRA. All TEAEs will be presented in a by-patient listing and summarized using System Organ Class and Preferred Term.

System Organ Class will be sorted alphabetically and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class and Preferred Term. System Organ Class and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class only or Preferred Term only.

- (1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (2) Treatment-Emergent Adverse Events by Preferred Term
- (3) Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (4) Product-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (5) Conditioning Chemotherapy-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (6) Study Procedure-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (7) Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (8) Grade 3 or higher Product-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term
- (9) Grade 3 or higher Conditioning Chemotherapy-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term
- (10) Toxicity Grade of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (11) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (12) Serious Product-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- (13) Treatment-Emergent Adverse Events Leading to Dose Rate Reduced by System Organ Class and Preferred Term
- (14) Treatment-Emergent Adverse Events Leading to Drug Withdrawn by System Organ Class and Preferred Term
- (15) Treatment-Emergent Adverse Events Leading to Dose Infusion Interrupted by System Organ Class and Preferred Term
- (16) Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term

- (17) Treatment-Emergent Adverse Events of Immune effector cell-associated neurotoxicity syndrome by System Organ Class and Preferred Term
- (18) Treatment-Emergent Adverse Events of Cytokine release syndrome by System Organ Class and Preferred Term
- (19) Treatment-Emergent Adverse Events of Hemophagocytic lymphohistiocytosis by System Organ Class and Preferred Term
- (20) Treatment-Emergent Adverse Events of Macrophage Activation Syndrome by System Organ Class and Preferred Term
- (21) Treatment-Emergent Adverse Events of Tumor Lysis Syndrome by System Organ Class and Preferred Term
- (22) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any grade and Grade ≥ 3)
- (23) Most Frequent Product-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any grade and Grade ≥ 3)
- (24) Most Frequent Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (10)

A subject with multiple occurrences of TEAE within a System Organ Class will be counted only once in that System Organ Class. A subject with multiple occurrences of TEAE within a Preferred Term will be counted only once in that Preferred Term.

- Summary tables for (10)

A subject with multiple occurrences of TEAE within a System Organ Class or a Preferred Term will be counted only once for the TEAE with the maximum toxicity grade.

- Summary tables for (22) and (23).

Most frequent TEAEs refer to Preferred Terms whose percentages are at least 10.0% in any one of the dose cohorts.

- Summary tables for (24).

Most frequent Non-Serious TEAEs refer to Preferred Terms whose percentages are at least 5.0% in any one of the dose cohorts. If no Non-Serious TEAEs exceed a frequency of 5.0%, the frequency cut-off of 2.0% will be used.

6.6.1.4 Overview of Conditioning Chemotherapy-Emergent Adverse Events

Analysis Set:

All Subjects Who Received Conditioning Chemotherapy

Analysis Variables:

Conditioning Chemotherapy-Emergent Adverse event

Categories:

Relationship to Conditioning Chemotherapy [Related, Not Related]

Relationship to Study Procedure [Related, Not Related]

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided for each dose cohort and overall.

(1) Overview of Conditioning Chemotherapy-Emergent Adverse Events

- 1) All Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 2) Conditioning Chemotherapy/Study Procedure-Related Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 3) Relationship of Conditioning Chemotherapy-Emergent Adverse Events to Conditioning Chemotherapy (number of events, number and percentage of subjects)
- 4) Relationship of Conditioning Chemotherapy-Emergent Adverse Events to Study Procedure (number of events, number and percentage of subjects)
- 5) Grade 3 or higher Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 6) Grade 3 or higher Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 7) Grade 3 or higher Study Procedure-Related Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 8) Toxicity Grade of Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 9) Serious Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)

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- 10) Conditioning Chemotherapy/Study Procedure-Related Serious Conditioning Chemotherapy-Emergent Adverse Events (number of events, number and percentage of subjects)
- 11) Relationship of serious Conditioning Chemotherapy-Emergent Adverse Events to Conditioning Chemotherapy (number of events, number and percentage of subjects)
- 12) Relationship of serious Conditioning Chemotherapy-Emergent Adverse Events to Study Procedure (number of events, number and percentage of subjects)
- 13) Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Delayed (number of events, number and percentage of subjects).
- 14) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Delayed (number of events, number and percentage of subjects).
- 15) Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Reduced (number of events, number and percentage of subjects).
- 16) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Reduced (number of events, number and percentage of subjects).
- 17) Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Rate Reduced (number of events, number and percentage of subjects).
- 18) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Rate Reduced (number of events, number and percentage of subjects).
- 19) Conditioning Chemotherapy-Emergent Adverse Events Leading to Drug Withdrawn (number of events, number and percentage of subjects).
- 20) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events Leading to Drug Withdrawn (number of events, number and percentage of subjects).
- 21) Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Infusion Interrupted (number of events, number and percentage of subjects).
- 22) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events Leading to Dose Infusion Interrupted (number of events, number and percentage of subjects).
- 23) Conditioning Chemotherapy-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

Events will be counted according to the rules below.

Number of subjects

- Summaries for 3), 4), 11) and 12)

A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 8)

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 3), 4), 8), 11) and 12)

A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

6.6.1.5 *Displays of Conditioning Chemotherapy-Emergent Adverse events*

Analysis Set:

All Subjects Who Received Conditioning Chemotherapy

Analysis Variable(s):

Conditioning Chemotherapy-Emergent Adverse event

Analytical Method(s):

The following summaries will be provided using frequency distribution.

Conditioning Chemotherapy-Emergent Adverse events will be coded using the MedDRA. All Conditioning Chemotherapy-Emergent Adverse events will be presented in a by-patient listing and summarized using System Organ Class and Preferred Term.

System Organ Class will be sorted alphabetically and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class and Preferred Term. System Organ Class and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class only or Preferred Term only.

- (1) Conditioning Chemotherapy-Emergent Adverse Events by System Organ Class and Preferred Term
- (2) Conditioning Chemotherapy-Related Conditioning Chemotherapy-Emergent Adverse Events by System Organ Class and Preferred Term
- (3) Grade 3 or higher Conditioning Chemotherapy-Emergent Adverse Events by System Organ Class and Preferred Term

Number of subjects

A subject with multiple occurrences of Conditioning Chemotherapy-Emergent Adverse event within a System Organ Class will be counted only once in that System Organ Class. A subject with multiple occurrences of Conditioning Chemotherapy-Emergent Adverse event within a Preferred Term will be counted only once in that Preferred Term. Percentages will be based on the number of all subjects who received conditioning chemotherapy.

6.6.1.6 *Overview of Pretreatment Events*

Analysis Set:

All Subjects Who Entered the Pretreatment Phase

Analysis Variables:

PTE

Categories:

Relationship to Study Procedure [Related, Not Related]

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided for each dose cohort and overall.

- (1) Overview of Pretreatment Events
 - 1) All Pretreatment Events (number of events, number and percentage of subjects)
 - 2) Relationship of Pretreatment Events to Study Procedure (number of events, number and percentage of subjects)
 - 3) Grade 3 or higher Pretreatment Events (number of events, number and percentage of subjects)
 - 4) Grade 3 or higher Study Procedure-Related Pretreatment Events (number of events, number and percentage of subjects)
 - 5) Toxicity Grade of Pretreatment Events (number of events, number and percentage of subjects)

- 6) Serious Pretreatment Events (number of events, number and percentage of subjects)
- 7) Relationship of serious Pretreatment Events to Study Procedure (number of events, number and percentage of subjects)
- 8) Pretreatment Events Leading to Dose Delayed (number of events, number and percentage of subjects).
- 9) Pretreatment Events Leading to Dose Reduced (number of events, number and percentage of subjects).
- 10) Pretreatment Events Leading to Dose Rate Reduced (number of events, number and percentage of subjects).
- 11) Pretreatment Events Leading to Drug Withdrawn (number of events, number and percentage of subjects).
- 12) Pretreatment Events Leading to Dose Infusion Interrupted (number of events, number and percentage of subjects).
- 13) Pretreatment Events Resulting in Death (number of events, number and percentage of subjects)

Events will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 7)

A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 5)

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 2), 5) and 7)

A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

6.6.1.7 *Displays of Pretreatment events*

Analysis Set:

All Subjects Who Entered the Pretreatment Phase

Analysis Variable(s):

PTE

Analytical Method(s):

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA. All PTEs will be presented in a by-patient listing and summarized using System Organ Class and Preferred Term.

System Organ Class will be sorted alphabetically and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class and Preferred Term. System Organ Class and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class only or Preferred Term only.

(1) Pretreatment Events by System Organ Class and Preferred Term

Number of subjects

A subject with multiple occurrences of PTE within a System Organ Class will be counted only once in that System Organ Class. A subject with multiple occurrences of PTE within a Preferred Term will be counted only once in that Preferred Term. Percentages will be based on the number of all subjects who entered the pretreatment phase.

6.6.2 Adverse Events of Clinical Interest

6.6.2.1 Displays of Treatment-Emergent ICANS/CRS Signs and Symptoms

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Treatment-Emergent ICANS Signs and Symptoms

Treatment-Emergent CRS Signs and Symptoms

Analytical Method(s):

The following summaries will be provided using frequency distribution.

Treatment-Emergent signs and symptoms will be coded using the MedDRA and will be summarized using System Organ Class and Preferred Term.

System Organ Class will be sorted alphabetically and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class and Preferred Term. System Organ Class and Preferred Term will be sorted in decreasing frequency for tables provided by System Organ Class only or Preferred Term only.

- (1) Signs and Symptoms by System Organ Class and Preferred Term
- (2) Grade 3 or higher Signs and Symptoms by System Organ Class and Preferred Term

Number of subjects

A subject with multiple occurrences of signs/symptoms within a System Organ Class will be counted only once in that System Organ Class. A subject with multiple occurrences of signs/symptoms within a Preferred Term will be counted only once in that Preferred Term. Percentages will be based on the number of all subjects in the safety analysis set.

6.6.3 Clinical Laboratory Evaluations

6.6.3.1 Hematology, Serum Chemistry and Coagulation

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Hematocrit, Hemoglobin, Leukocytes, Lymphocytes, Monocytes, Eosinophils, Basophils, Neutrophils, Platelets count

Serum Chemistry

Albumin, ALP, ALT, AST, Total bilirubin, BUN, Calcium, Bicarbonate, Chloride, Standard C-reactive protein, Creatine, CPK, Gamma Glutamyl Transferase (GGT), Glucose, LDH, Magnesium, Phosphorus, Potassium, Sodium, Ferritin, Urate, Amylase, Lipase

Coagulation

APTT, Prothrombin time, Fibrinogen

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit:

Hematology/Serum Chemistry

Screening, Conditioning Chemotherapy, Baseline, Day 2, Day 4, Day 8, Day 11, Day 15, Day 18, Day 22, Day 29, Month 3, Month 4, Month 5, Month 7, Month 10, Month 13, Month 19, Month 25, Month 31, Month 37

Coagulation

Screening, Conditioning Chemotherapy, Baseline, Day 2, Day 4, Day 8, Day 15, Day 22, Day 29, Month 3, Month 4, Month 5, Month 7, Month 10, Month 13, Month 37

Analytical Methods:

For each variable, summaries (1) and (2) will be provided by dose cohort and overall.

For applicable variables, summary (3) will be provided by dose cohort and overall.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-dose visit - Baseline) will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by NCI CTCAE 5.0 will be provided.

6.6.3.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Turbidity	[Abnormal, Normal]
Color	[Abnormal, Normal]
Bilirubin	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Glucose	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Ketones	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Leukocytes	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Nitrite	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Occult blood	[-, +/-, 1+, 2+, 3+, 4+, 5+]
pH	
Protein	[-, +/-, 1+, 2+, 3+, 4+, 5+]
Specific gravity	
Urobilinogen	[-, +/-, 1+, 2+, 3+, 4+, 5+]

Categories:

Toxicity Grade	[Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]
----------------	---

Visit:

Screening, Conditioning Chemotherapy, Baseline, Day 8, Day 15, Day 22, Day 29,
Month 3, Month 4, Month 7, Month 13, Month 37

Analytical Methods:

For pH and specific gravity, summaries (1) and (2) will be provided by dose cohort and overall.

For each variable other than pH and specific gravity, summary (3) will be provided by dose cohort and overall.

For applicable variables, summary (4) will be provided by dose cohort and overall.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-dose visit - Baseline) will be provided for each visit.

(2) Case Plots of Urine Laboratory Test Results

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-dose visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by NCI CTCAE 5.0 will be provided.

6.6.4 Vital Signs and Weight

Analysis Set:

Safety Analysis Set

Analysis Variables:

Systolic Blood Pressure

Diastolic Blood Pressure

Heart Rate

Body Temperature

Weight

Visit:

Vital Signs

Screening, Leukapheresis, Conditioning Chemotherapy, Baseline, Day 1 Post, Day 1 6 Hours, Day 2 Timepoint 1, Day 2 Timepoint 2, Day 4, Day 8, Day 11, Day 15, Day 18, Day 22, Day 29, Month 3, Month 4, Month 5, Month 7, Month 10, Month 13, Month 19, Month 25, Month 31, Month 37

Weight

Screening, Conditioning Chemotherapy, Baseline, Day 8, Day 15, Day 22, Day 29, Month 3, Month 4, Month 5, Month 7, Month 10, Month 13, Month 19, Month 25, Month 31, Month 37

Analytical Methods:

For each variable, summaries (1) to (2) will be provided by dose cohort and overall.

For applicable variables, summary (3) will be provided by dose cohort and overall.

(1) Summary for Vital Signs Parameters and Weight and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-dose visit - Baseline) will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

6.6.5 12-Lead ECGs

Analysis Set:

Safety Analysis Set

Analysis Variables:

ECG Ventricular Rate

RR Interval

PR Interval

QRS Interval

QT Interval

QTcF Interval

QTcB Interval

Interpretation

[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit:

Screening, Baseline, Day 29

Analytical Methods:

For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by dose cohort and overall.

For applicable variables, summary (3) will be provided by dose cohort and overall.

For 12-lead ECG interpretation, summary (4) will be provided by dose cohort and overall.

(1) Summary of 12-lead ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of 12-lead ECG Parameters

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by NCI CTCAE 5.0 will be provided.

(4) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result will be provided.

6.6.6 Other Safety Analysis

6.6.6.1 ECOG Performance Status

Analysis Set:

Safety Analysis Set

Analysis Variables:

ECOG Performance Status [0, 1, 2, 3, 4]

Analytical Methods:

(1) Summary of Shift of ECOG Performance Status

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result will be provided.

6.6.6.2 *Number and percentage of cases with RCR-positive test results*

Analysis Set:

Safety Analysis Set

Analysis Variables:

RCR [Positive, Negative]

Visits:

Baseline, Month 4, Month 7, Month 13, Month 19, Month 25, Month 31, Month 37

Analytical Methods:

The following summaries will be provided by dose cohort and overall.

(1) Number and Percentage of Subjects with Positive RCR

The number and percentage of RCR positive subjects at pre- and post-TAK-103 infusion will be provided.

(2) Number and Percentage of Subjects with Positive RCR by Visit

Frequency distributions for RCR will be provided for each visit.

6.6.6.3 *SpO₂*

Analysis Set:

Safety Analysis Set

Analysis Variables:

SpO₂

Visit:

Screening, Conditioning Chemotherapy, Baseline, Day 1 Post, Day 1 6 Hours, Day 2 Timepoint 1, Day 2 Timepoint 2, Day 4, Day 8

Analytical Methods:

Summaries (1) and (2) will be provided by dose cohort and overall.

(1) Summary for SpO₂ and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each post-dose visit - Baseline) will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

6.6.7 Extent of Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total CAR-T cell number of TAK-103 administered (cells/body)

Total amount of conditioning chemotherapy converted to BSA (mg/m^2)

Analytical Methods:

- (1) Summary of total CAR-T cell number of TAK-103 administered

Descriptive statistics will be provided by dose cohort and overall.

- (2) Summary of total amount of conditioning chemotherapy converted to BSA

Descriptive statistics will be provided by dose cohort and overall for each medication (Cyclophosphamide or Fludarabine).

6.7 Cellular Kinetics, Pharmacodynamic, and Biomarker Analysis

Blood samples will be collected and analyzed for TAK-103 transgenes copies per genomic DNA by ddPCR and TAK-103 cell number by flow cytometry at pre-dose and various timepoints (as listed in protocol SOE) post TAK-103 infusion for primary analysis.

Individual blood levels of TAK-103 and TAK-103 cell number versus time data will be listed by dose level or indication using the CK analysis set. Individual blood levels of TAK-103 and TAK-103 cell number versus actual time profiles will be plotted on both linear and semi-logarithmic scales for each subject using the CK analysis set.

Blood levels of TAK-103 and TAK-103 cell numbers will be summarized by nominal time points for each dose-level and indication using the following descriptive statistics including n, arithmetic mean, standard deviation, percent coefficient of variation (CV%), median, minimum, and maximum. Blood level of TAK-103 and TAK-103 cell numbers will be reported to 3 significant figures in summary statistics except for CV% which will be reported to 1 decimal place.

Blood level of TAK-103 and TAK-103 cell number concentrations that are below the limit of quantification (BLQ) will be set to zero for calculation of summary statistics. [REDACTED]

[REDACTED]

CK parameters will be estimated using non-compartmental methods with Phoenix® WinNonlin® and population-based approach by NONMEM 7 (ICON plc, Dublin, Ireland). The actual sampling and dose duration times will be used for calculation of the CK parameters. As permitted by the data, CK parameters will be estimated from the blood level of TAK-103 and TAK-103 cell number versus time profiles using the CK analysis set as the following:

CK Parameter	Definition
$C_{\max}$	The maximum observed concentration of TAK-103
$T_{\max}$	The time at which post TAK-103 infusion, the $C_{\max}$ occurred
AUC_{last}	Area under the concentration versus time curve (AUC) from time 0 to the last quantifiable measurement, calculated using the linear trapezoidal rule
$AUC_{(0-28)}$	AUC from time 0 to 28 days after TAK-103 infusion (Day 29)
$AUC_{(0-90)}$	AUC from time 0 to 90 days after TAK-103 infusion (Month 4)
C_{28}	Measurement at 28 days after TAK-103 infusion (Day 29)
C_{last}	The last quantifiable measurement
T_{last}	The last quantifiable time point
α	TAK-103 contraction rate constant
β	TAK-103 expansion rate constant
TauM	Differentiation rate constant to memory cell, and memory cell death rate constant
DeltaM	Memory cell death rate constant

CK parameters will be summarized using descriptive statistics. The CK parameters will be determined, as permitted by data and will be evaluated by dose level, indication, and mesothelin expression levels (Mesotheline TPS scpre (%)), tumor burden and responder/non-responder (including CR, PR, SD, and PD) status.

The detailed CK/pharmacodynamic analysis (using biomarkers such as IFNg, IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, IL-13, and tumor necrosis factor alpha) will be presented separately in a Clinical Pharmacology Analysis Plan (CPAP) as well as population CK analysis plan.

6.8 Other Analyses

6.8.1 Immunogenicity Analysis

Analysis Set:

Immunogenicity-evaluable Analysis Set

Analysis Variables:

Anti-CAR-ECD ADA [Positive, Negative]

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Visit:

Screening, Day 15, Day 29, Month 3, Month 4, Month 5, Month 7, Month 10, Month 13, Month 19, Month 25, Month 31, Month 37

Analytical Methods:

The following summaries will be provided.

(1) Number of Subjects with ADA

The number and percentage of subjects with positive ADA for each visit will be provided by dose cohort and overall. The number and percentage of subjects with positive ADA after TAK-103 administration will also be provided.

(2) Summary of ADA Titer by Visit

For subjects with positive ADA, descriptive statistics for ADA titer will be provided for each visit by dose cohort and overall.

(3) Box plots of ADA Titer by Visit

For subjects with positive ADA, box plots of ADA titer will be presented for each visit by dose cohort and overall.

(4) Case plots

Plots of ADA titer over time for each subject will be presented. For subjects with negative ADA, ADA values will be treated as 0.

The effect of immunogenicity on CK parameters, safety, and efficacy may also be examined.

6.9 Interim Analyses

No formal interim analysis is planned in this study. The investigator and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort.

7.0 REFERENCES

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The analyses described in the statistical analysis plan do not differ from those specified in the protocol.

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9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

The changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
5.3 CK Analysis Set	Patients with sufficient dosing and CK data to reliably estimate 1 or more CK parameters will be used for CK analyses.	<i>Patients who have received any dose of TAK-103 and have at least 1 CK parameter estimated will be used for CK analysis.</i>	Definition of the CK Analysis Set has been modified for clarity and to follow the definition in the study protocol.
5.6 Immunogenicity-evaluable Analysis Set	Patients from the safety analysis set who have baseline and at least 1 postbaseline immunogenicity assessment.	New section.	The Immunogenicity-evaluable Analysis Set has been added for the analyses of the immunogenicity data and to follow the definition in the study protocol.
6.6.1.1 Overview of Treatment-Emergent Adverse Events	(2) Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects) (9) Grade 3 or higher Study Procedure-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects) (12) Product/Conditioning Chemotherapy/Study Procedure-Related Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)	New text.	Summaries added to further describe the AE data.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	<p>(14) Relationship of serious Treatment-Emergent Adverse Events to Conditioning Chemotherapy (number of events, number and percentage of subjects)</p> <p>(15) Relationship of serious Treatment-Emergent Adverse Events to Study Procedure (number of events, number and percentage of subjects)</p>		
6.6.1.3 Displays of Treatment-Emergent Adverse Events	(3) Product/Conditioning Chemotherapy/Study Procedure-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	New text.	Summaries added to further describe the AE data.
6.6.1.4 Overview of Conditioning Chemotherapy-Emergent Adverse Events	New section.	New text.	Summaries added to further describe the AE data.
6.6.1.6 Overview of Pretreatment Events	New section.	New text.	Summaries added to further describe the AE data.
6.6.4 Vital Signs and Weight	<p>Categories</p> <p>Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]</p> <p>(3) Summary of Shifts of Vital Signs Parameters</p> <p>Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by NCI CTCAE 5.0 will be provided.</p>	Text deleted.	Text relating to toxicity grade not relevant for vital signs.
6.6.7 Extent of Extent of Exposure and Compliance	Total CAR-T cell number of TAK-103	New text.	Summaries added to further describe the extent

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	administered (cells/body) Total amount of conditioning chemotherapy converted to BSA (mg/m²) (1) Summary of total CAR-T cell number of TAK-103 administered Descriptive statistics will be provided by dose cohort and overall. (2) Summary of total amount of conditioning chemotherapy converted to BSA Descriptive statistics will be provided by dose cohort and overall for each medication (Cyclophosphamide or Fludarabine).		of exposure and compliance data.
6.7.1 Pharmacodynamic Analysis	Entire section.	Text deleted.	Text describing pharmacodynamic analyses moved to separate CPAP.
6.8.1 Immunogenicity Analysis	Safety Analysis Set.	Immunogenicity-evaluable Analysis Set.	Analysis set changed as it is more appropriate to summarize the immunogenicity data using the immunogenicity-evaluable Analysis Set rather than the Safety Analysis Set.

9.2 Data Handling Conventions

9.2.1 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered TAK-103 infusion. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. When calculating Study Day relative to a reference date (i.e., date of first dose [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be

calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

9.2.2 Definition of Visit Windows

All evaluable data (i.e., non-missing data) will be handled according to the following rules.

Most data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF) (see the footnote of the following visit window table).

For each visit, the observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

Baseline will be defined as Day 1 Pre or Conditioning Chemotherapy if Day 1 Pre is not scheduled, unless stated otherwise.

Table 9.a Visit Window of Hematology/Serum Chemistry

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 2*	Study Day: 2	-
Day 4	Study Day: 4	3 - 6
Day 8	Study Day: 8	7 - 9
Day 11	Study Day: 11	10 - 13
Day 15	Study Day: 15	14 - 16
Day 18	Study Day: 18	17 - 19
Day 22	Study Day: 22	20 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 $(= (3-1)*30+1)$.

Table 9.b Visit Window of Coagulation

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 2*	Study Day: 2	-
Day 4	Study Day: 4	3 - 6
Day 8	Study Day: 8	7 - 11
Day 15	Study Day: 15	12 - 18
Day 22	Study Day: 22	19 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 $(= (3-1)*30+1)$.

Table 9.c Visit Window of Urinalysis Tests

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 8	Study Day: 8	5 - 11
Day 15	Study Day: 15	12 - 18
Day 22	Study Day: 22	19 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 13, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 $(= (3-1)*30+1)$.

Table 9.d Visit Window of Vital Signs

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Leukapheresis*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 1 Post*	Study Day: 1	-
Day 1 6 hours*	Study Day: 1	-
Day 2 Timepoint 1*	Study Day: 2	-
Day 2 Timepoint 2*	Study Day: 2	-
Day 4	Study Day: 4	3 - 6
Day 8	Study Day: 8	7 - 9
Day 11	Study Day: 11	10 - 13
Day 15	Study Day: 15	14 - 16
Day 18	Study Day: 18	17 - 19
Day 22	Study Day: 22	20 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 ($= (3-1)*30+1$).

Table 9.e Visit Window of Weight and ECOG performance status

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 8	Study Day: 8	5 - 11
Day 15	Study Day: 15	12 - 18
Day 22	Study Day: 22	19 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

Table 9.e Visit Window of Weight and ECOG performance status

Visit	Scheduled Study Day (days)	Time Interval (days)
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* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 ($= (3-1)*30+1$).

Table 9.f Visit Window of 12-Lead ECGs

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Baseline (Conditioning Chemotherapy*)	Study Day: -	-
Day 29	Study Day: 29	22 - 36

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

Table 9.g Visit Window of RCR-positive test results

Visit	Scheduled Study Day (days)	Time Interval (days)
Baseline (Conditioning Chemotherapy*)	Study Day: -	-
Month Y (Y=4, 7, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 4 is 91 ($= (4-1)*30+1$).

Table 9.h Visit Window of SpO₂

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Conditioning Chemotherapy*	Study Day: -	-
Baseline (Day 1 Pre*)	Study Day: 1	-
Day 1 Post	Study Day: 1	-
Day 1 6 hours	Study Day: 1	-

Table 9.h Visit Window of SpO₂

Visit	Scheduled Study Day (days)	Time Interval (days)
Day 2 Timepoint 1*	Study Day: 2	-
Day 2 Timepoint 2*	Study Day: 2	-
Day 4	Study Day: 4	3 - 6
Day 8	Study Day: 8	7 - 9

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF)

Table 9.i Visit Window of Serum Concentrations of Pharmacodynamics

Visit	Scheduled Study Day (days)	Time Interval (days)
Conditioning Chemotherapy*	Study Day: -	-
Day 1 Pre*	Study Day: 1	-
Day 1 Post*	Study Day: 1	-
Day 2*	Study Day: 2	-
Day 4	Study Day: 4	3 - 6
Day 8	Study Day: 8	7 - 9
Day 11	Study Day: 11	10 - 13
Day 15	Study Day: 15	14 - 16
Day 18	Study Day: 18	17 - 19
Day 22	Study Day: 22	20 - 24
Day 29	Study Day: 29	25 - 33
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 $(= (3-1)*30+1)$.

Table 9.j Visit Window of Immunogenicity

Visit	Scheduled Study Day (days)	Time Interval (days)
Screening*	Study Day: -	-
Day 15	Study Day: 15	8 - 22
Day 29	Study Day: 29	23 - 35

Table 9.j Visit Window of Immunogenicity

Visit	Scheduled Study Day (days)	Time Interval (days)
Month Y (Y=3, 4, 5)	Study Day: XX**	Scheduled Study Day $\pm$ 14
Month Y (Y=7, 10, 13, 19, 25, 31, 37)	Study Day: XX**	Scheduled Study Day $\pm$ 28

* Data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

** Study day XX of month Y is calculated as $(Y-1)*30+1$. For example, scheduled study day of Month 3 is 61 ($= (3-1)*30+1$).

9.2.3 Conventions for handling of missing/partial dates

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication started (or stopped) prior to or after TAK-103 infusion. The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to January 1;
- If only Day is missing, then set to the first of the month;

If end date of a medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to December 31;
- If only Day is missing, then set to last day of the month;

If start date or end date of a medication is completely missing, do not impute.

9.2.4 Examples of iPD date per iRECIST

iPD date is defined as follows:

- If iUPD is subsequently confirmed (i.e. followed by iCPD), the first iUPD date is used as iPD date (Example 1)
- If iUPD is not subsequently confirmed,
 - If a subsequent iSD, iPR or iCR is seen then the initial iUPD is ignored (Example 2 and 4)
 - Otherwise the iUPD date is used as iPD date (Example 3)

	TP 1	TP 2	TP 3	TP 4	TP 5	iPD date
Example 1	iUPD	iUPD	iCPD			TP 1
Example 2	iPR	iPR	iUPD	iPR	iPR	Not occurred
Example 3	iPR	iUPD	iUPD	NE	NE	TP 2
Example 4	iUPD	iPR	iSD	iUPD	iCPD	TP 4

9.3 Analysis Software

All statistical analyses will be conducted using SAS® Version 9.4 or higher.

Signature Page for 16-1-9-1 Statistical Analysis Plan 2024-06-10

Title: TAK-103-1001 Statistical Analysis Plan 2024-06-10

Approval

Document Number: DN-000384063 v2.0

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