Statistical Analysis Plan

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Title: A Phase 1/2a, Open-Label, Dose Escalation, and Dose Expansion Study to Assess the Safety and Efficacy of GDX012 in Patients With Relapsed or Refractory Acute Myeloid Leukemia

Study Number: TAK-012-1501

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-012-1501

A Phase 1/2a, Open-Label, Dose Escalation, and Dose Expansion Study to Assess the Safety and Efficacy of GDX012 in Patients With Relapsed or Refractory Acute Myeloid Leukemia

Phase: 1/2a

Version: 2.0

Date: 16 September 2025

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ABBREVIATIONS

AE	adverse event
AML	acute myeloid leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BM	bone marrow
BOIN	Bayesian Optimal Interval
BOP2	Bayesian optimal phase 2
CK	cellular kinetic(s)
C_{max}	maximum observed concentration
CR	complete response
CRh	complete response with partial hematologic recovery
CRhMRD-	CR with partial hematologic recovery without MRD
CRi	complete response with incomplete hematologic recovery
CRiMRD-	CR with incomplete hematologic recovery without MRD
CRF	case report form
CRMRD-	complete remission without MRD
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EQ-5D-5L	European Quality of Life-5-Dimensions-5 Levels
FDA	[United States] Food and Drug Administration
γδ	gamma delta
GvHD	graft-versus-host disease
HLA	human leukocyte antigen
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
MLFS	morphological leukemia free state
MRD	Measurable residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
OS	overall survival

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PD	pharmacodynamics
PR	partial response
PRO	patient reported outcome
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
STR	short tandem repeat
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
Vδ1	variable delta 1 chain
WHO	World Health Organization

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1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objectives

- To evaluate safety and tolerability and establish the RP2D of GDX012 in adult patients with relapsed or refractory (R/R) AML.

1.1.2 Secondary Objectives

- To evaluate disease response and efficacy in adult patients with R/R AML who received GDX012.

1.1.3 Exploratory Objectives

- To evaluate the cellular kinetics (expansion and persistence) of GDX012 in blood.
- To evaluate the immunogenicity of GDX012.
- To evaluate the presence of GDX012 in bone marrow.
- To explore the relationship between exposure and response (safety, disease response, and product attributes) using exposure/response analysis and cellular kinetic (CK) /pharmacodynamic (PD) modelling, where feasible.
- To evaluate the level of cytokines and soluble factors in blood after GDX012 administration.
- To evaluate any correlations between exploratory biomarkers, disease response, and safety of GDX012.
- To assess healthcare resource utilization.
- To establish health utility.

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1.2 Endpoints

1.2.1 Primary Endpoints

- Incidence of dose-limiting toxicities (DLTs), maximum tolerated dose (MTD).
- Incidence of TEAEs, including SAEs and clinically significant laboratory values.

1.2.2 Secondary Endpoint(s)

- Disease response including complete response (CR), CR with partial hematologic recovery (CRh), CR with incomplete hematologic recovery (CRi), morphological leukemia-free state (MLFS), and partial response (PR).
- Measurable residual disease (MRD) by flow cytometry. MRD negative state defined by <0.1% detectable disease based on local assessment of bone marrow and/or blood.

- Duration of response (DOR).
- Event-free survival (EFS).
- OS.

1.2.3 Exploratory Endpoint(s)

- Measurement of circulating cytokines, chemokines, and other soluble immune mediators in blood for safety and as markers of cellular activation.
- Immunophenotyping of HSC, γδ T-cells, and tumor cells in blood and/or bone marrow aspirate to correlate to response.
- Ribonucleic acid (RNA) analysis of bone marrow (BM) aspirate to profile tumor cells, their susceptibility to innate killing mechanisms and bone marrow inflammatory environment.
- Measurement of GDX012 CK (expansion and persistence) in blood over time and infiltration of GDX012 in bone marrow.
- Maximum observed concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), persistence (time of last measurable concentration above the lower limit of quantitation), area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}), and other parameters as appropriate.
- Immunogenicity by assessment of anti-HLA donor specific antibodies.
- MRD by next generation sequencing (NGS).
- Collection of healthcare resource utilization data.
- Calculation of health utility values as measured with the European Quality of Life-5-Dimensions-5 Levels (EQ-5D-5L) questionnaire.

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2.0 STUDY DESIGN

This is a phase 1/2a, dose escalation and dose expansion study of the safety, tolerability, and efficacy of GDX012 in adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML).

The study will be conducted in 2 phases.

Phase 1: A sequential dose escalation guided by a Bayesian optimal interval (BOIN) design ([1], [2], [3]) will be used to select the recommended phase 2 dose (RP2D). The maximum sample size for dose escalation is approximately 18 patients for 3 planned dose levels.

Expansion of an existing dose level and stopping the dose escalation early may be permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety, or for a better understanding of the dose related toxicity, exposure, and/or pharmacodynamics (PD). Other non-dose-limiting toxicity (DLT) safety data and available clinical, clinical pharmacology, or biomarker data will also be considered to inform subsequent

dose recommendations, dose escalation decisions, and potential maximum tolerated dose (MTD) elimination. At the end of phase 1, 1 or 2 dose levels will be selected for phase 2a based on safety, tolerability, preliminary antitumor activity, and cellular kinetics (CK) from the dose escalation phase.

Phase 2a: Dose expansion will be performed to further evaluate safety and tolerability, CK, PD, and efficacy. The dose expansion cohorts will be monitored using the Bayesian optimal phase 2 (BOP2) design [4].

- If 2 doses are selected from phase 1, initially 20 response-evaluable patients will be randomized in 1:1 fashion across the selected 2 dose levels from phase 1. An interim futility analysis is performed when the first 10 response-evaluable patients at each dose level have had the opportunity to be assessed for at least 1 disease response after last GDX012 administration. Only 1 dose level will be selected to continue the enrollment of 15 additional patients if not stopped for futility. The selection of the dose level following interim analysis is based on if exceeding the futility boundary and the totality of data.
- If only one dose is selected from phase 1, a total of 25 response-evaluable patients will be enrolled with an interim futility analysis performed once the first 10 response-evaluable patients have been assessed for at least 1 disease response after last GDX012 infusion.

The patients in the expansion cohorts may be adjusted to include patients from the dose escalation phase who were treated at the same dose level.

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3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The expected total number of patients to be enrolled in the study is approximately 53.

Phase 1: Approximately 18 DLT-evaluable patients will be treated at 1 of 3 planned dose levels of $V\delta1^+$ γδ T viable cells per patient (based on patient body weight).

Phase 2a: A maximum of 25 response-evaluable patients for 1 dose level and 35 response-evaluable patients for 2 dose levels will be enrolled following BOP2 design. Such sample size will allow a statistical power of 77.3% to distinguish between an active therapy with a true response rate of 50% from a therapy with a response rate of 30% or less, while controlling the type I error rate at 0.094. Approximately 10 to 20 patients may be enrolled in the exploratory cohort(s) to explore alternative conditioning regimen or dose schema.

5.0 ANALYSIS SETS

5.1 Intent-to-treat (ITT) set

All enrolled patients in this GDX012 study. This set will be used for demographic summary of patients.

5.2 Safety analysis set

Patients who have received GDX012 administration. This set will be used for safety analyses and for some efficacy analyses at phase 2a.

5.3 DLT-evaluable analysis set

Patients who were infused with a full dose of GDX012 and who were monitored for toxicities during the first 30 days post infusion. Participants removed from the study due to a DLT during the DLT evaluation period will be included in the DLT-evaluable population. Patients who withdrew before completing the DLT assessment period for reasons other than a DLT will be replaced in the cohort. The DLT-evaluable population will be used to guide dose escalation decision and estimate MTD at phase 1.

5.4 Response-evaluable analysis set

Patients who have received GDX012 administration, have had morphologic disease at baseline, and at least 1 posttreatment assessment of disease response, or were discontinued due to disease progression or death before the first posttreatment disease assessment. This set will primarily be used for analyses of disease response at phase 2a.

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5.5 CK analysis set

Patients receiving treatment with GDX012 administration and having sufficient data to estimate 1 or more CK parameters will be used for CK analyses.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values are defined as the last observed value prior to the first dose of lymphodepleting chemotherapy unless specified otherwise.

Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Screen failure subjects will be grouped and listed at the end.

All the endpoints in phase 1 and phase 2a will be summarized by dose levels separately, unless specified otherwise.

The data from the patients who received a second dose of GDX012 will be analyzed separately.

6.1.1 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which they were collected unless otherwise specified. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

6.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of lymphodepleting chemotherapy. Otherwise, the 15th of the month will be used.
- If only the year is present, and it is the same as the year of the first dose of lymphodepleting chemotherapy, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of lymphodepleting chemotherapy, the 15th of June will be used, unless other data indicates that the date is earlier.

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6.1.3 Conventions for Partial or Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing.
  - If month and year are the same as month and year of the first GDX012 infusion date, then impute to the first GDX012 infusion date.
  - If month and year are different than month and year of the first GDX012 infusion date, then impute to first day of the month.
- If year is known but day and month are missing.
  - If year is same as year of the first GDX012 infusion date, then the first GDX012 infusion date will be used instead.
  - If year is different than year of the first GDX012 infusion date, then 1st of January of the year will be imputed.
- If all are missing, then the start date is imputed with the first GDX012 infusion date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the stop dates to ensure the stop date does not occur before start date.

Adverse events with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing:
  - If YYYY < year of the last GDX012 infusion date, then 31st of December will be imputed.
  - If YYYY = year of the last GDX012 infusion date, then 31st of December will be imputed.
  - If YYYY > year of the last GDX012 infusion date, then 1st of January will be imputed.
- If all are missing, then impute date to 31st of December, in the year of the last GDX012 infusion.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date. If subject dies, then use death date for AE stop date.

6.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month.
- If year is known, but day and month are missing, then 1st of January of the year will be imputed.
- If all is missing, then impute date to Date of Birth (DOB).
- If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB).

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing:
  - If YYYY < year of the last GDX012 infusion date, then 31st of December will be imputed.
  - If YYYY = year of the last GDX012 infusion date, then 31st of December will be imputed.
  - If YYYY > year of the last GDX012 infusion date, then 1st of January will be imputed.

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- If all is missing, then impute date to 31st of December in the year of the last GDX012 infusion.

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If a subject dies, the death date will be used for the concomitant therapies stop date. After the imputation, all imputed dates will be checked against the start dates to ensure stop date did not occur before start date. If the imputed stop date occurs prior to start date, then the imputed date will be the same as the start date.

6.1.5 Conventions for Partial or Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing:
  - If the onset month and year are the same as the month and year of the last GDX012 infusion date, the day of the last GDX012 infusion date + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of the last GDX012 infusion date, the first day of the month will be imputed.
- When only a year is present,
  - If the onset year is the same as the year of the last GDX012 infusion date, the date of the last GDX012 infusion date + 1 will be imputed.
  - If the onset year is not the same as the year of the last GDX012 infusion date, the first day of the year is imputed.
- If no components of the onset date are present, the date of the last GDX012 infusion date + 1 will be imputed.

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6.1.6 Conventions for Partial or Missing Death Dates

- If death year and month are available, but day is missing:
  - If the year and month for the last date known to be alive are the same as the year and month of death date, death date will be the day after the last date known to be alive.
  - If the year and month for the last date known to be alive is earlier than the year and month of death date, death date will be the first day of the death month.
- If both month and day are missing for death date or a death date is completely missing, do not impute, and censor the subject survival time at the last date known to be alive.

6.2 Disposition of Subjects

The number of subjects screened, enrolled, treated with lymphodepleting chemotherapy and treated with GDX012 will be summarized. The number of subjects in each analysis set will be

provided. The reasons for discontinuing treatment and discontinuing study will also be summarized.

The summary will be presented by dose levels in phase 1 and phase 2a, overall for phase 1 and phase 2a, and overall for the study.

The percentages will be based on the number of patients in the safety population, except for the number of subjects screened, enrolled, and treated with lymphodepleting chemotherapy.

For the screening phase, the clinical eligibility criteria that were not met by patients will also be tabulated. The number of subjects enrolled by site will also be summarized.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Demographics will be summarized by dose levels in phase 1 and phase 2a, overall for phase 1 and phase 2a, and overall for the study using the safety analysis set. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters, as appropriate. Age will be calculated from date of birth to date of informed consent.

Throughout this study, baseline assessments are defined as those performed at the closest time on or prior to the start of lymphodepleting chemotherapy, unless specified otherwise.

Disease characteristics will also be summarized in a similar fashion. Time since initial diagnosis will also be summarized.

Continuous variables will be summarized by means, medians, standard deviations, and ranges; categorical variables will be summarized by counts and percentages. Other variables may also be included in this analysis by categorizing the continuous variables or re-categorizing existing categorical variables.

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6.4 Medical History and Concomitant Medications

Medical history and concomitant medications will be analyzed in the safety analysis set by each phase. A general medical history will be listed for all patients, with medical history defined as any start date prior to informed consent.

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from screening through the end of the on-study period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO generic drug term and sorted in decreasing frequency based on the number of reports. A patient who has been administered several medications with the same preferred medication name will be counted only once. The preferred medication name will be used.

6.5 Any Prior Interventions

6.5.1 Prior Anti-cancer Therapy

Types of prior anticancer therapy will be summarized by regimen types, along with number of lines, and best overall response to prior anticancer therapies.

Types of prior stem cell transplant and source of stem cells will be summarized.

6.5.2 Other Prior Interventions

A listing of prior surgery or procedure will be provided.

6.6 Efficacy Analysis

6.6.1 Primary Efficacy Endpoint Analysis

Not applicable. Efficacy is not the primary endpoint for this study.

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6.6.2 Secondary Efficacy Endpoint(s) Analysis

The analysis of the secondary efficacy endpoints includes disease response, MRD negative rate, DOR, EFS, and OS.

6.6.2.1 Disease Response Rate and Objective Response Rate (ORR)

Analysis of disease response will be based on the response-evaluable population. Throughout this SAP, CR, CRh, and CRi with or without MRD- will be considered the same in efficacy analyses. The definitions regarding CR, CRh, and CRi in this SAP are presented in Table 6.a.

The disease response rate is defined as the proportion of subjects who achieve a best overall response of CR, CRh, or CRi, based on responses assessed by the investigator according to the 2022 ELN response criteria for AML.

ORR is defined as the proportion of subjects who achieve a best overall response of CR, CRh, CRi, MLFS, or PR, based on responses assessed by the investigator according to the 2022 ELN response criteria for AML.

The disease response rate or ORR and the associated 2-sided 95% CIs will be calculated using the Clopper-Pearson exact binomial method. Estimates of response rate will be used to guide interim futility analysis.

Table 6.a Definitions of CR, CRi, and CRh

Disease response	Definition
CR	The sum of Complete Remission (CR) and Complete Remission without MRD (CRMRD-)
CRh	The sum of CR with Partial Hematologic Recovery (CRh) and CR with Partial Hematologic Recovery without MRD (CRhMRD-)

CRi	The sum of CR with Incomplete Hematologic Recovery (CRi) and CR with Incomplete Hematologic Recovery without MRD (CRiMRD-)

6.6.2.2 Best Overall Response (BOR)

BOR is defined as the best response from the initial GDX012 infusion until the last evaluable assessment, derived from responses assessed by the investigator according to the 2022 ELN response criteria for AML, and recorded on or before the earliest of: (i) refractory or relapsed disease (after CR, CRh, or CRi); (ii) initiation of subsequent anti-cancer therapy; or (iii) withdrawal of consent. Subsequent anti-cancer therapy may include anti-cancer medication, cancer-related surgery, or stem cell transplant.

Subjects with no adequate or no evaluable disease response assessment after the initial GDX012 treatment will be assigned as Not Evaluable (NE).

The number and percentage of subjects in each category of derived BOR will be summarized.

6.6.2.3 MRD negative rate

MRD negative rate will also be estimated with a 2-sided 95% exact binomial confidence interval using response-evaluable population. MRD negative state is defined by <0.1% detectible disease at any visit.

6.6.2.4 DOR

DOR is defined only for patients who experience a CR, CRh, or CRi and is the time from the date of first documented CR, CRh, or CRi to the date of first documented relapse or death from any cause, whichever comes first. Patients not meeting the criteria for relapse from CR, CRh, or CRi nor death will be censored at the last disease assessment. Detailed handling rules for missing assessments and censoring for the analysis for DOR are presented in Table 6.b.

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Table 6.b Handling of Missing Assessments and Censoring for DOR Analysis

Situation	Date of event or censoring	Outcome
Relapse from CR, CRh, or CRi	Date of relapse from CR, CRh, or CRi	Event
No documented relapse or death	Date of last adequate disease assessment [a]	Censored
Lost to follow-up, withdraw consent before any documented relapse or death	Date of last adequate disease assessment [a]	Censored
Relapse from CR, CRh, or CRi or death happened after more than 1 missing disease assessments visit	Date of last adequate disease assessment before missing more than 1 consecutive assessments	Censored
SCT started before documented relapse or death	Date of last adequate disease assessment [a] before SCT	Censored
Death before first disease assessment	Date of death	Event
Death between adequate disease assessment visits	Date of death	Event

[a] Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

DOR will be analyzed using Kaplan-Meier method for patients who experience a CR, CRh, or CRi, using relapse or any-cause death as events.

6.6.2.5 EFS

The analysis of EFS will be based on the safety analysis set. EFS is defined as the time from the date of the first GDX012 administration to the date of treatment failure, relapse for those who have CR, CRh, or CRi, or death from any cause, whichever comes first. Treatment failure is defined as failure to achieve CR, CRh, or CRi at the first disease assessment after the last GDX012 infusion.

For patients who achieve treatment success and are alive and in remission at the data cut-off, EFS should be censored at the last assessment date. As the SCT treatment is integral to the practice of medicine, the analysis of the time-to-event endpoint EFS will be conducted without censoring for SCT. Detailed handling rules for missing assessments and censoring will follow Table 6.c.

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Table 6.c Handling of Missing Assessments and Censoring for EFS Analysis

Situation	Date of event or censoring	Outcome
No postbaseline disease assessment, and no death	Date of the first GDX012 administration	Event
Treatment Failure	Date of the last GDX012 administration	Event
Relapse from CR, CRh, or CRi	Date of relapse from CR, CRh, or CRi	Event
No documented EFS event	Date of last adequate disease assessment [a]	Censored
Lost to follow-up, withdraw consent before any documented EFS event	Date of last adequate disease assessment [a]	Censored
Relapse from CR, CRh, or CRi or death happened after more than 1 missing disease assessments visit	Date of last adequate disease assessment before missing more than 1 consecutive assessments.	Censored
Death before first disease assessment	Date of death	Event
Death between adequate disease assessment visits	Date of death	Event

[a] Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

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EFS will be analyzed descriptively using Kaplan-Meier method.

6.6.2.6 OS

The analysis of OS will be based on the safety analysis set. OS is defined as the time from the date of the first GDX012 administration to the date of death from any cause. Patients who do not die will be censored at the last contact date.

OS will be analyzed descriptively using Kaplan-Meier method.

6.7 Safety Analysis

6.7.1 Adverse Events

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated. Safety will be summarized separately for phase 1 and phase 2a unless otherwise specified.

Treatment-emergent adverse events (TEAEs) are defined as any AE that begins on or after the administration of lymphodepleting chemotherapy.

AEs will be tabulated for the following observation periods:

- Pretreatment: the period from signed informed consent to the day before lymphodepleting chemotherapy.

- Treatment: the period from administration of lymphodepleting chemotherapy to end of study.

TEAEs will also be tabulated separately for the period between lymphodepleting chemotherapy and GDX012 administration and the period after GDX012 administration.

- Before GDX012: any AE that begins on or after the administration of lymphodepleting chemotherapy but before the infusion of GDX012
- After GDX012: any AE that begins on or after the start date of GDX012.

The incidence and percentages of TEAEs will be summarized by System Organ Class and Preferred Term of the ICH Medical Dictionary for Regulatory Activities and by grade according to the NCI CTCAE version 5.0. In addition, grading of CRS and ICANS will follow the ASTCT guidelines [5], grading of acute GvHD will follow the recommendations by the Mount Sinai Acute GvHD International Consortium [6] and grading of chronic GvHD will follow the 2014 NIH Consensus [7]. For each set of grading criteria, a later version of the criteria may be applied.

Tabulated AEs will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- The most commonly reported TEAEs (i.e., those events reported by ≥10% of patients).
- SAEs.
- Drug-related SAEs.
- Deaths.
- Drug-related deaths.
- Adverse events of clinical interest as defined in 6.7.2.

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The incidence of DLTs will be tabulated by dose level using the DLT evaluable population.

AE will be summarized separately for patients who received a second dose of GDX012.

6.7.2 Adverse Events of Clinical Interest

The sponsor has designated some AEs as being of clinical interest. Due to the limited clinical exposure to GDX012, there are no known risks. Nonclinical laboratory testing has not identified any serious risks. Potential risks are based on the experiences of patients receiving other cellular therapies. GDX012 is expected to have a lower toxicity profile than therapies utilizing αβ T-cells.

The list of AECI includes:

- Acute or chronic Graft-versus-host disease (GVHD)

- Hypersensitivity reactions
- CRS
- ICANS
- bone marrow aplasia or need for stem cell rescue
- Tumor lysis syndrome
- New primary malignancy

These TEAEs of clinical interest are defined using SMQs, HLTs, and/or individual Preferred Terms, as clinically appropriate.

The analyses of TEAEs of clinical interest will be conducted using the safety analysis set, as similar fashion described in Section 6.7.1.

6.7.3 Other Safety Analysis

Descriptive statistics for the actual values of clinical laboratory parameters will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and ECGs will be tabulated by scheduled time point. ECOG performance scores will also be summarized using shift tables.

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6.7.4 Extent of Exposure and Compliance

The exposure to [redacted] will be characterized by total amount of dose received (mg), total number of doses received, and relative dose intensity using safety set. The number and percentage of patients whose dose was modified or discontinued will be summarized.

The relative dose intensity (%) is defined as: 100 *(total dose received)/(total dose intended). Total dose intended is the summation of the intended doses on Days -5, -4 and -3.

The exposure to GDX012 will be characterized by total number of γδ T-cells in prepared product, total number and percentage of $V\delta1^+$ cells in prepared product, the percentage of $\gamma\delta^+$ in prepared product, total number of γδ T-cells infused to patients, total number and percentage of $V\delta1^+$ cells infused to patients, the percentage of $\gamma\delta^+$ infused to patients, and viability in the prepared product using safety set.

The exposure will be summarized separately by dose levels.

6.8 CK Analysis

Blood samples will be collected and analyzed for GDX012 using the following:

- Flow cytometry for $V\delta1^+$ γδ T-cells.

- STR-based chimerism assay to assess for the presence of donor cells.

on Day -5, Day 1 at Pre-dose, 1 hour (±10 minutes), and 3 hours (±10 minutes) after GDX012 administration, Day 2, Day 4, Day 5, Day 8, Day 11, Day 14, Day 21, Day 30, Day 45, Day 60, and Day 100 for primary analysis.

Individual blood level of GDX012 (donor/recipient DNA proportions from STR based chimerism assay and cell number from the flow cytometry assay) versus time data will be listed by dose level using the CK analysis set. Individual blood level of GDX012 and GDX012 cell number versus actual time profiles will be plotted on both linear and semi logarithmic scales for each subject using the CK set.

Blood levels of GDX012 (donor/recipient DNA proportions from STR based chimerism assay and cell number from the flow cytometry assay) will be summarized by nominal time point for each dose level using the following descriptive statistics includes n, arithmetic mean, SD, percent coefficient of variation (CV%), median, minimum and maximum. Blood level of GDX012 will be reported in percentage with 1 decimal number due to STR based chimerism assay's low sensitivity and GDX012 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 GDX012 (donor/recipient DNA proportions from STR based chimerism assay and cell number from the flow cytometry assay) that are below the limit of quantification (BLQ) will be set to zero for calculation of summary statistics.

CK parameters will be estimated using noncompartmental methods by Phoenix® WinNonlin® (Certara L.P., Princeton, NJ) Version 8.0 or higher. The actual sampling and dose duration times will be used for the calculation of CK parameters. As permitted by data, CK parameters will be estimated from the measurement of total Vδ1+ γδ T-cells in blood as measured by flow cytometry and/or donor-recipient DNA proportions as measured by an STR-based chimerism assay, using the CK analysis set as the following.

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CK Parameter	Definition
C_{max}	The maximum observed measurement
t_{max}	The time at which 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 Day 28 post dose
$AUC_{(0-90)}$	AUC from time 0 to Month 3 post dose
C_{28}	Measurement at Day 28
C_{last}	The last quantifiable measurement
T_{last}	The last quantifiable time point

For the calculation of CK parameters, all BLQ will set to missing except that prior to the first measurable value will be set to zero. The BLQ values that are between measurable values will be set to missing.

Individual CK concentration-time data and individual CK parameters will be listed and also summarized as permitted by data by dose cohort using descriptive statistics: the n, arithmetic mean, SD, CV%, minimum, median, maximum, and geometric mean and geometric CV%. T_{max} will be summarized by n, minimum, median, and maximum only. In addition, the impact of product quality data on CK parameters will be investigated as well. The assessment of GDX012 CK will be used to examine the exposure-response relationship, as well as the possible correlation of persistence (T_{last}) and expansion (C_{max}) of GDX012 with safety and disease response endpoints.

CK parameters will be reported to 3 significant figures in summary statistics except for CV% and geometric CV%, which will be reported to 1 decimal place.

Descriptions of modeling methods about generation of CK slope parameters and data analysis will be documented and reported in a separate brief report.

6.9 Immunogenicity Analyses

Frequency and percentage of patients with detectable donor specific anti-HLA antibody will be summarized by scheduled time point using the safety analysis set. Impact of donor specific anti-HLA immunogenicity on CK parameters, safety and efficacy may be assessed, as appropriate based on the available data.

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6.10 Exploratory Analyses

6.10.1 Population CK-Pharmacodynamic Analysis

The relationship between GDX012 systemic exposure and safety, efficacy, and pharmacodynamic response (eg, changes in cytokines/chemokines, etc.) will be evaluated to understand the CK-pharmacodynamic relationship of GDX012. These data will be reported outside the CSR.

6.10.2 Biomarker Analyses

Exploratory biomarker analyses will be separately defined in biomarker analysis plan and the results of these analyses may be reported separately from the CSR.

6.10.3 PRO Analyses

All PRO analyses will use the safety analysis set. In this study, generic HRQoL will be evaluated using the EQ-5D-5L questionnaire.

6.10.3.1 Compliance

The percentage of compliance for PRO completions based on the safety analysis set will be summarized over time. At each visit when the questionnaire was scheduled to be completed, the percentage of patients who completed at least one item of the EQ-5D-5L questionnaire will be calculated overall and by site; the percentage of patients who completed all items in the EQ-5D-

5L will also be calculated overall and by site. The denominator will be the number of patients who are still in the study at that visit with respective denominators.

6.10.3.2 Descriptive Statistics

Descriptive analyses will be conducted, and the following statistics will be reported as appropriate (n, median, 25th percentile, 75th percentile, minimum, maximum, mean, standard deviation) in the safety analysis set for all PRO analyses. The number of patients who contributed to each time point will be summarized for each table, including the proportion missing for each question.

6.10.3.3 EQ-5D-5L Analysis

Analyses of EQ-5D-5L will be exploratory and will be summarized using descriptive statistics. A listing of the frequency of values for each of the 5 dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be presented. A summary table of the number of patients who selected "severe" or "unable/extreme" (i.e., the highest level of problems) will be presented for each time point. The raw value and absolute change from baseline of the EQ-5D-5L VAS score at time of last visit and time to deterioration will be presented by dimension.

6.10.4 Healthcare Resource Utilization Analyses

Healthcare resource utilization will be summarized using descriptive statistics in the safety analysis set. Healthcare utilization data will be summarized in descriptive statistics of medical encounters, inpatient days and the number of missing days from work or other activities as reported by patient and caregiver. Further modeling may be performed separately in post hoc analyses.

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6.11 Statistical Considerations for Dose Escalation During Phase 1

Dose escalation of GDX012 will follow BOIN design ([1], [2], [3]) to inform dose escalation decisions and potential MTD estimation. The target toxicity rate for the MTD is 0.3 and the maximum sample size is approximately 18 for 3 dose levels. Each dose level will enroll at least 3 patients. As shown in Table 6.d, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation.

- If the observed DLT rate at the current dose is ≤0.236, escalate the dose to the next higher dose level; if the current dose is the highest dose, treat the new patients at the highest dose.
- If the observed DLT rate at the current dose is >0.359, de-escalate the dose to the next lower dose level; if the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary (as shown in Table 6.d), at which point the dose escalation will be terminated for safety.
- Otherwise, stay at the current dose.

- Repeat above until the maximum sample size of 18 is reached, or until the number of evaluable patients treated at the current dose reaches 6 and the decision according to above is to stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.3 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level $j, j = 1, 2, 3$.

Table 6.d Dose Escalation/De-escalation Rule for the BOIN Design

Number of evaluable patients treated	1	2	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2
Deescalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5

BOIN: Bayesian optimal interval; DLT: dose-limiting toxicity.

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

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Expansion of an existing dose level and stopping the dose escalation early may be permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety, or for a better understanding of the dose-related toxicity, exposure, and/or pharmacodynamics. Other non-DLT safety and available clinical, CK, or biomarker data will also be considered to inform subsequent dose recommendations, dose escalation decisions, and potential MTD estimation.

At the end of phase 1, 1 or 2 dose levels may be selected for phase 2a based on safety, tolerability, efficacy, and CK from the dose escalation phase.

6.11.1 Backfill Patient in the Dose Escalation Phase

Any dose escalation cohort not exceeding the MTD can be expanded to a maximum of 10 patients for further evaluation of safety, CK, PD, and preliminary antitumor activity of GDX012 after discussion between the investigators and sponsor. Only patients meeting the inclusion criteria will be enrolled into backfill. The added patients will provide additional data to enable the selection of recommended doses for expansion.

6.12 Interim Analysis and Criteria for Early Termination

The dose expansion cohorts will follow the BOP2 design with the maximum sample size for 1 dose level as 25 response-evaluable patients.

Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the response rate and define the null hypothesis $H_0: p_{eff} \leq 0.3$, under which the treatment is deemed as unacceptable. We may stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.3|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.85 and α=0.74 are design parameters optimized to maximize power (i.e., the probability of correctly claiming that the treatment is acceptable under H_1) under the alternative hypothesis $H_1: p_{eff} = 0.5$, while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.094. This optimization is performed assuming a vague prior Beta(0.3,0.7) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.773 under H_1:

Table 6.e Optimized Stopping Boundaries

Number of Patients Treated	Stop if # Responses ≤
10	2
25	10

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The go/no-go criteria in Table 6.e are non-binding. Based on Table 6.e, we will perform an interim futility analysis when the number of enrolled response evaluable patients reaches 10 and those patients have had the opportunity to be assessed for at least 1 disease response after last GDX012 infusion. The decision rules will be used along with the overall safety, tolerability, efficacy, CK, and PD information, to make recommendations whether to terminate a specific cohort at phase 2a or continue development at end of phase 2a.

Below are the operating characteristics (Table 6.f) of the design using the BOP2 web application (BOP2 V1.4.12.0), which is available at http://www.trialdesign.org.

Table 6.f Operating Characteristics

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.20	67.78	0.53	14.8
2	0.25	52.56	2.83	17.1
3	0.30	38.28	9.38	19.3
4	0.40	16.73	40.13	22.5
5	0.50	5.47	77.29	24.2
6	0.60	1.23	95.85	24.8

6.13 Data Monitoring Committee

An independent data monitoring committee (IDMC) will be convened in phase 2a of this study in accordance with Takeda standard operating procedures and the guidance set forth by the FDA as described in the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. The IDMC Chair will review reported SAEs every 3

months. The IDMC will review safety and efficacy data (for futility analysis only) and be chartered to make study conduct recommendations based on an analysis of risk versus benefit.

Details of the IDMC will be captured in a separate charter.

7.0 REFERENCES

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

NA

9.0 APPENDIX

SAS version 9.4 or higher will be used for the analysis.

Signature Page for 16-1-9-1 Statistical Analysis Plan v2.0
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