Clinical Study Protocol

NCT Number: NCT05886491

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

Document Version and Date: Initial protocol, 13 Jan 2023

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PROTOCOL

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

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Ave Lexington, MA 02421 Please note: Takeda Development Center Americas, Inc. (TDC Americas) may be referred to in this protocol as "sponsor" or "Takeda."
Study Number:	TAK-012-1501
IND Number:	027397
EudraCT Number:	Not Applicable
Compound:	GDX012 (also known as TAK-012)
Date:	13 January 2023

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

[redacted]

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1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

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[redacted] MD Date
[redacted], Cellular Therapies

[redacted], PhD Date
[redacted], Cellular Therapies

[redacted], PhD Date
[redacted], Cellular Therapies

[redacted] PhD Date
[redacted], Cellular Therapies

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	13-Jan-2023 12:55 UTC
[redacted]	Clinical Approval	13-Jan-2023 13:55 UTC
[redacted]	Clinical Pharmacology Approval	13-Jan-2023 13:55 UTC
[redacted]	Biostatistics Approval	13-Jan-2023 14:48 UTC

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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

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Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** GDX012 (also known as TAK-012)
Title of Protocol: 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	**IND No.:** 027397 **EudraCT No.:** Not Applicable
Study Number: TAK-012-1501	**Phase:** 1/2a

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 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. 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. If neither of the 2 dose cohorts is stopped for the futility, only 1 dose level will be selected to continue the enrollment of 15 additional patients based on the totality of data. If only 1 dose is selected from phase 1, a total of 25 patients will be enrolled with an interim futility analysis performed when the first 10 response-evaluable patients have had the opportunity to be assessed for at least 1 disease response after the last GDX012 administration. 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.

An alternative conditioning regimen or dose schema, with approximately 10 to 20 patients may be enrolled separately.

Patients with R/R AML will be asked to sign the study informed consent form (ICF) before undergoing screening for the study. Patients who sign the ICF and meet the protocol-defined eligibility criteria following screening will be enrolled. Patients who do not meet the protocol-defined eligibility criteria will be screen failures.

Screening assessments must be performed within 21 days of starting lymphodepleting chemotherapy (Day -5).

Eligible patients will undergo lymphodepleting chemotherapy with [redacted] 30 mg/m^2/day IV for 3 days (Day -5 to Day -3) and [redacted] 500 mg/m^2/day IV for 3 days (Day -5 to Day -3) followed by infusion of GDX012 on Day 1.

During phase 1, patients will be hospitalized for observation for at least 3 days after GDX012 infusion and may subsequently be discharged at the investigator's discretion. If no acute toxicities are observed during phase 1, patients in phase 2a may be discharged at the investigator's discretion following the GDX012 infusion.

Patients will have the following study visits for assessment of eligibility, safety, efficacy, CK, and biomarkers:

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screening; lymphodepleting chemotherapy (Days -5 to -3); GDX012 infusion (Day 1); immediate post-infusion monitoring (Day 1 through Day 4); and post-infusion assessments on Days 5, 8, 11, 14, 17, 21, 30, 60, and 100. A BM assessment on Day 45 is required for patients without count recovery at Day 30. The window for evaluating patients for DLTs will be 30 days following infusion of GDX012.

For cohort 1, there will be at least a 30-day interval between dosing for all patients, including any replacement for early withdrawal and additional patients required under the BOIN design rules. For cohorts 2 and 3, there will be at least a 30-day interval between dosing the first and second patient only. Staggered dosing is not required for all subsequent patients, including any additional patients required under the BOIN design rules. For the dose expansion phase (phase 2a), no interpatient dosing interval is required.

The clinical cutoff to evaluate safety will occur once all patients have been followed for at least 100 days after last GDX012 infusion or until they have died or withdrawn from the study. After the Day 100 assessments, patients will be followed for survival and persistence of response at 6, 9, and 12 months after last GDX012 infusion. Disease status and anticancer therapies captured as part of standard of care will be documented in the electronic case report form (eCRF) at these timepoints.

Patients who achieve a response (ie, complete response [CR], complete response with incomplete hematologic recovery [CRi], complete response with partial hematologic recovery [CRh], morphological leukemia-free state [MLFS], or partial response [PR]) based on 2022 European LeukemiaNet (ELN) response criteria for AML from the initial GDX012 infusion and do not experience a DLT, and are healthy enough to undergo a second lymphodepletion, may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion. A second dose will be preceded by a de-intensified lymphodepleting chemotherapy regimen and will follow the same assessment schedule as the initial dose. For patients who continue on to a second dose, no more than 30 days may elapse between completion of disease evaluation and start of lymphodepletion.

The overall study schema for TAK-012-1501 is illustrated in Figure 6.a.

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Primary Objective:

- To evaluate safety and tolerability and establish the RP2D of GDX012 in adult patients with R/R AML.

Secondary Objective:

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

Patient Population: Adult patients with confirmed R/R AML. During phase 1, patients must be ineligible for hematopoietic stem cell transplantation (HSCT) due to a comorbid condition, inability to receive HSCT conditioning, lack of an available donor, the patient having declined procedure after documented discussion of the risks and benefits, or the investigator considers it not to be in the best interest of the patient.

Number of Patients:	**Number of Sites:**
Phase 1: Approximately 18 patients will be enrolled. ***Phase 2a:*** Approximately 35 patients will be enrolled.	Approximately 15 sites across the United States.

Investigational Therapy:

GDX012 suspension for IV infusion is an allogeneic cell therapy that is enriched for variable delta 1 chain ($V\delta1^+$) gamma delta ($\gamma\delta$) T-cells.

Three dose levels of GDX012 will be tested in phase 1. Dose levels will be adjusted to 2 body weight ranges; patients weighing [redacted] and weighing [redacted] as follows:

[redacted]

Administration of investigational therapy will be preceded by lymphodepleting chemotherapy consisting of IV [redacted] (30 mg/m^2 body surface area [BSA] per day) and [redacted] (500 mg/m^2 BSA per day) on Days -5, -4, and -3.

Patients who achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on 2022 ELN response criteria for AML from the initial GDX012 infusion at Day 30, do not experience a DLT, and are healthy enough to undergo a second lymphodepletion may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion.

A second dose will be preceded by a de-intensified 3-day lymphodepletion regimen consisting of IV [redacted] (25 mg/m^2 BSA per day) and [redacted] (300 mg/m^2 BSA per day) and will follow the same assessment schedule as the initial dose. For patients who continue on to a second dose, no more than 30 days may elapse between completion of disease evaluation and start of lymphodepletion.

Period of Evaluation:

Study enrollment: Approximately 26 months.

***Core study (conditioning phase + treatment and primary follow-up phase)*:**
Patients will be followed-up for at least 100 days after last GDX012 infusion, death, or withdrawal from the study.

Secondary follow-up phase: After completion of the primary follow-up phase, patients will be followed every 3 months for up to 12 months after the last GDX012 infusion.

Main Criteria for Inclusion:

1. Aged ≥18 years at the time of signing the informed consent.
2. Total body weight of ≥40 kg.
3. Must have pathologically confirmed R/R AML per 2022 International Consensus Classification (ICC), as follows:
   a. Relapsed AML is defined as the appearance of ≥5% blasts in the bone marrow (BM) or peripheral blood at any time after achieving a CR, CRh, CRi, or MLFS.
   b. Refractory AML is defined as failure to achieve a CR, CRh, CRi, or MLFS after 1 of the following regimens:
      i. i. Two courses of intensive induction chemotherapy, eg, 7+3 (7 days of cytarabine plus 3 days of anthracycline); mitoxantrone, etoposide, and cytarabine; high-dose cytarabine; etc. (where 5+2 given on Days 14 to 21 for persistent leukemia on Day 14 will count as a second induction or 1 induction attempt is required for patients >60 years of age.
      ii. At least 2 cycles of a hypomethylating agent (HMA) or low-dose, cytarabine-based combination regimen including, but not limited to, venetoclax or other B-cell lymphoma 2 (BCL2) inhibitors.
      iii. At least 4 cycles of HMA monotherapy.

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4. During dose escalation, patients must be ineligible for HSCT due to comorbid condition, inability to receive HSCT conditioning, lack of an available donor, patient having declined procedure after documented discussion of the risks and benefits, or investigator considers it not to be in the best interest of the patient.
5. Must have an anticipated life expectancy of >3 months before lymphodepletion.
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1.
7. Left ventricular ejection fraction of ≥40% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan.
8. Adequate organ function as indicated by the laboratory values below:

System	Laboratory Value
Coagulation:	
• Platelet count	• $\geq 30 \times 10^9$/L (transfusion allowed)
• Prothrombin time or international normalized ratio	• ≤1.5 × upper limit of normal (ULN) unless receiving therapeutic or prophylactic anticoagulation
• Partial thromboplastin time	• ≤1.5 × ULN unless receiving therapeutic or prophylactic anticoagulation
Hematology:	
• Hemoglobin	• ≥7.0 g/dL (transfusion allowed)
Renal:	
• Calculated or measured creatinine clearance [a]	• ≥30 mL/min
Hepatic:	
• Serum total bilirubin	• ≤1.5 × ULN (higher levels are acceptable if these can be attributed to active hemolysis (as indicated by positive Coomb's test result, decreased haptoglobin, documented Gilbert's disease, elevated indirect bilirubin, and/or lactate dehydrogenase) or ineffective erythropoiesis (as indicated by bone marrow findings)
• Alanine aminotransferase	• ≤2.5 × ULN
• Aspartate aminotransferase	• ≤2.5 × ULN

a. Renal function (creatinine clearance or surrogate estimated glomerular filtration rate) will be estimated or measured according to standard practice at the treating institution.

9. Female patients who:
   a. Are postmenopausal for at least 1 year before the screening visit, or
   b. Are surgically sterile, or
   c. If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through at least 12 months following GDX012 administration, or
   d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and

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e. Agree not to breastfeed a baby or donate an egg or eggs (ova) during the study and until at least 12 months following GDX012 administration.

10. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    a. Agree to practice effective barrier contraception from the time of signing the informed consent through at least 12 months following GDX012 administration, or
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and
    c. Agree not to donate sperm during the study and at least until 12 months following GDX012 administration.
11. Voluntary written informed consent before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Willingness and ability to comply with scheduled visits and study procedures.

Main Criteria for Exclusion:

1. Diagnosis of acute promyelocytic leukemia.
2. Has received or plans to receive any of the following excluded therapy/treatment within the specified timeframe before lymphodepleting chemotherapy:
    a. Cytotoxic chemotherapy or immunotherapy within 2 weeks before lymphodepletion. Hydroxyurea is allowed up to 2 days before start of lymphodepletion. Intrathecal chemotherapy is allowed up to 7 days before lymphodepletion. Hypomethylating agents are allowed up to 10 days before lymphodepletion.
    b. Corticosteroids or any other immunosuppressive therapy within 2 weeks before lymphodepletion, with exception of the following:
        i. Use of inhaled, topical, intranasal, ocular, or intra-articular corticosteroids.
        ii. Physiological doses of replacement steroids (eg, for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent.
    c. Investigational treatment or interventional clinical trial within 2 weeks or 5 half-lives (if known), whichever is longer, before lymphodepletion.
    d. Major surgery within 4 weeks before lymphodepletion (patients must have fully recovered from any surgery-related toxicities).
    e. Donor lymphocyte infusion within 30 days before lymphodepletion for patients who have previously undergone HSCT.
3. Prior allogeneic HSCT within 3 months of signing ICF or with ongoing requirement for systemic graft-versus-host therapy.
4. Has received prior gene or modified cell therapy (eg, chimeric antigen receptor T-cell [CAR-T] or chimeric antigen receptor natural killer [CAR-NK]).
5. White blood cell count >20,000/μL or evidence of rapid disease progression that would prevent completion of at least 1 dose cycle. (Cytoreductive therapies including leukapheresis or hydroxyurea are allowed.)
6. Ongoing nonhematologic toxicity from prior anticancer therapy that has not recovered to Grade ≤1 before enrollment (except for nonclinically significant toxicities, eg, alopecia, vitiligo), with the exception of patients with Grade 2 toxicities that are deemed stable or irreversible (eg, hypothyroidism), who may be enrolled at the investigator's discretion.
7. Known hypersensitivity to [redacted], or other agents, or excipients used in the study.
8. History of chronic or recurrent (within the last year before screening) severe autoimmune or immune-mediated disease requiring steroids or other immunosuppressive treatments, including antitumor necrosis factor agents.

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9. Active central nervous system involvement (eg, symptomatic, central nervous system [CNS] 3, or radiologically detected disease). Patients with history of CNS leukemia which has been adequately treated will be considered eligible.
10. History or presence of active/clinically relevant CNS disorder such as seizure, encephalopathy, cerebrovascular ischemia/hemorrhage, severe dementia, cerebellar disease, or any autoimmune disease with CNS involvement. For CNS disorders that recover or are in remission, patients without recurrence within 2 years of planned study enrollment may be included.
11. History of malignancy are excluded with the following exceptions:
    a. Patients with a history of treated non-melanoma skin cancer, or in situ carcinoma of cervix, bladder, or breast who have received curative treatment anytime before screening.
    b. Patients with low-grade, early stage prostate cancer (eg, Gleason score ≤6, stage 1 or 2) with no requirement for therapy at anytime before enrollment.
    c. Any other malignancy status post curative intent therapy and in remission without treatment for ≥2 years before enrollment.
    d. Patients on adjuvant endocrine therapy for localized hormone receptor positive breast cancer for ≥2 years before enrollment.
12. Uncontrolled intercurrent illness including, but not limited to, the following:
    a. Ongoing or active infection (eg, requiring systemic antimicrobial therapy for treatment of infection within 5 days before start of lymphodepletion). Patients on long-term antimicrobial therapy with no evidence of active disease and those on prophylactic antimicrobial therapy are not excluded.
    b. Clinically significant cardiac disease defined by congestive heart failure New York Heart Association Class 3 or Class 4.
    c. Clinically significant (symptomatic) cardiac arrhythmias (eg, sustained ventricular tachycardia, second- or third-degree atrioventricular block without a pacemaker, or circulatory collapse arrhythmia requiring therapy).
    d. Acute coronary syndrome (unstable angina or myocardial infarction) in the last 6 months. Patients with medically controlled angina may be enrolled.
    e. Interstitial lung disease causing patient to be oxygen therapy dependent.
13. Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) as defined below:
    a. Positive serology for HIV.
    b. Positive hepatitis B surface antigen (HBsAg) test and/or positive HBV deoxyribonucleic acid (DNA) test. Patients who are HBsAg negative but are hepatitis B core antibody positive must have undetectable HBV DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated before lymphodepleting therapy and continued for 6 months.
    c. Positive HCV ribonucleic acid (RNA) test. Patients who are hepatitis C antibody positive will be screened for HCV RNA by any reverse transcription PCR or branched DNA assay. If hepatitis C antibody is positive, eligibility will be determined based on a negative screening RNA value.
14. Clinically active severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) viral infection defined by prior positive test or presumptive symptoms without demonstration of a negative test.
15. Female patients who are lactating and breastfeeding.
16. Female patients who have a positive serum pregnancy test.
17. Any other medical, psychological, or social condition that, in the opinion of the principal investigator, would contraindicate the patient's participation in the clinical study due to safety or compliance with clinical study procedures.

Endpoints:

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Primary Endpoints:

- Incidence of DLTs, MTD.
- Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and clinically significant laboratory values.

Secondary Endpoints:

- Disease response including CR, CRh, CRi, MLFS, and PR.
- Measurable residual disease (MRD) by flow cytometry. The MRD negative state is defined by <0.1% detectable disease based on local assessment of bone marrow and/or blood.
- Duration of response (DOR).
- Event-free survival (EFS).
- Overall survival (OS).

Statistical Considerations:

The dose escalation will follow BOIN design. DLT-evaluable participants are defined as those participants who were infused with 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 withdraw before completing the DLT assessment period for reasons other than a DLT will be replaced in the cohort.

The dose expansion cohorts will follow the BOP2 design with the maximum sample size for 1 dose level as 25 response-evaluable patients. 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 infusion. At most, 1 dose level will be selected to continue the enrollment of 15 additional patients. The selection of the dose level following interim analysis is based on the futility boundary and totality of data. If only 1 dose is selected from phase 1, a total of 25 patients are enrolled with an interim futility analysis performed when the first 10 response-evaluable patients have had the opportunity to be assessed for at least 1 disease response after last GDX012 infusion.

Adverse events will be monitored during the expansion cohorts. Accrual to the study will be suspended if:

- AEs defined in Section 8.7 meet the stopping bounds of number ≥2/5, ≥4/10, ≥6/15, ≥7/20, 9/25; or
- At any time if ≥1 patients present with fatal AEs at least possibly related to GDX012.

The stopping bounds for the above AEs are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rules are met, there is at least 70% probability that the true toxicity rate is greater than 30% with a prior beta distribution with parameters 1 and 1 for the binomially distributed toxicity rate.

Patient demographic and baseline characteristics will be summarized descriptively. 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. Treatment-emergent adverse events will also be tabulated separately for the period between lymphodepleting chemotherapy and GDX012 administration and the period after GDX012 administration.

Analysis of disease response will be based on the response-evaluable population which is defined as patients who receive GDX012, have a disease assessment at screening (baseline evaluation), and at least 1 postbaseline disease assessment or disease progression before the first posttreatment disease assessment. Estimates of the CR, CRh, CRi, MLFS, and PR will be presented with a 2-sided 95% exact binomial confidence intervals. DOR, EFS, and OS, if applicable, will be analyzed descriptively using the Kaplan-Meier method for phase 2a only. The MRD negative rate will also be estimated along with a 2-sided 95% exact binomial confidence intervals for phase 2a only.

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Sample Size Justification:

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

Phase 1: Approximately 18 DLT-evaluable patients at 1 of 3 planned GDX012 dose levels (based on patient body weight) will be enrolled.

Phase 2a: The dose expansion cohorts will follow the BOP2 design with a maximum of 25 response-evaluable patients for 1 dose level, and of 35 response-evaluable patients for 2 dose levels.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

Identified vendors will perform specific study related activities either in full or in partnership with the sponsor. The sponsor will perform all other study-related activities.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

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3.3 List of Abbreviations

ACT	adoptive cell therapy
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
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
B-ALL	B-cell acute lymphoblastic leukemia
BCL2	B-cell lymphoma 2
BM	bone marrow
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
BSA	body surface area
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cells
CARTOX	CAR T–cell therapy–associated TOXicity
CFR	Code of Federal Regulation
CK	cellular kinetic(s)
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRh	complete response with partial hematologic recovery
CRi	complete response with incomplete hematologic recovery
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival

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eGFR	estimated glomerular filtration rate
ELN	European LeukemiaNet
EMA	European Medicines Agency
EOS	end of study
EQ-5D-5L	European Quality of Life-5-Dimensions-5 Levels
FDA	[United States] Food and Drug Administration
FIH	first-in-human
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GFR	glomerular filtration rate
γδ	gamma delta
GvHD	graft-versus-host disease
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agent
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICC	International Consensus Classification
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IFNγ	interferon gamma
IL-	interleukin-
IND	Investigational New Drug
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous(ly)
MDRD	modification of diet in renal disease
MEC	mitoxantrone, etoposide and cytarabine
MHC	major histocompatibility complex
MLFS	morphological leukemia-free state
MRD	measurable residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Institute

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NCR	natural cytotoxicity receptor
NGS	next generation sequencing
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NK	natural killer (cells)
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PI	principal investigator
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
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
Th1	T helper 1 (cell)
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
TNFα	tumor necrosis factor alpha
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of the normal range
US	United States
Vδ1	variable delta 1 chain
WHO	World Health Organization

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3.4 Corporate Identification

Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC Americas	Takeda Development Center Americas, Inc
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Japan	Takeda Development Center Japan

4.0 INTRODUCTION

4.1 Disease Background

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, accounting for approximately 80% of cases in this group (Yamamoto and Goodman 2008). The incidence of AML increases with age, from approximately 3.1 cases per 100 000 population in patients less than 65 years old, to 18.3 cases per 100 000 population in those over 65 years in the United States (SEER 21, 2000-2017).

Despite greater molecular insights into the pathogenesis of AML and modest advances in treatment, >10 000 of the ~20 000 new patients with AML diagnosed in the United States each year die of their disease (Siegel et al. 2019). Relapse is the most common cause of treatment failure. The 5-year overall survival (OS) for adult patients with AML after disease relapse is only 10% (DeWolf and Tallman 2020). Furthermore, approximately 20% of patients demonstrate primary induction failure (Petersdorf et al. 2013) (Othus et al. 2015). Allogeneic hematopoietic stem cell transplantation is a potentially curative treatment, but is often associated with significant therapy-related toxicity and mortality. Overall survival (OS) is estimated at 15% to 25% 3 to 5 years post-transplant (Weisdorf 2016) (Christopeit et al. 2013). Many patients, especially those over the age of 65, are deemed unfit to receive intensive therapy for AML, further limiting response and survival (Kantarjian et al. 2006).

R/R AML has a very poor prognosis, thus there is a high unmet need for novel therapeutic approaches (Schmid et al. 2006).

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4.1.1 Current Treatment

Immunotherapy products have revolutionized the treatment of many cancers. However, despite advances in targeted therapies for certain AML subsets, the overall outcome for patients with AML remains poor. Several immunotherapy products such as bispecific antibodies, antibody drug conjugates, checkpoint inhibitors, and cellular products are under investigational development for the treatment of AML. Adoptive cell therapy (ACT) may provide an additional treatment option for patients and comprises the IV transfer of either autologous or allogeneic immune cells. Recent new drug approvals using CD19 targeting chimeric antigen receptor (CAR) T-cells for the treatment of B-cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkin's lymphoma (NHL) have generated tremendous interest for this strategy to treat other malignancies. Unfortunately, similar strategies such as those targeting CD33 and CD123 for the treatment of AML have not yielded the same success as approved CAR-T therapies in pediatric acute lymphoblastic leukemia, NHL and multiple myeloma and show an unfavorable toxicity profile due to the targeting of healthy myeloid progenitor cells (Tasian 2018).

Therefore, new strategies are needed to overcome toxicities (eg, on-target, cytokine release syndrome [CRS], neurotoxicity) and address antigen escape mechanisms and potential cellular exhaustion reported for most CAR T-cell therapies. While timely pharmacological intervention is effective in the management of most CAR T-cell toxicities, the development of next-generation

cell therapies with an improved safety profile remains an area of intense research. The addition of innate immune cell types such as natural killer (NK) cells and gamma delta (γδ) T-cells to the armamentarium of ACT may overcome the challenges observed with currently developed cell therapies.

4.1.2 GDX012

GDX012 suspension for IV infusion is a novel allogeneic cell therapy that is enriched for variable delta 1 chain ($V\delta1^+$) γδ T-cells developed for the treatment of hematological malignancies including AML. GDX012 is classified as a T-cell therapy product and the active substance is $V\delta1^+$ γδ T-cells. The potential clinical application of $V\delta1^+$ γδ T-cells as a cell therapy has been significantly inhibited by the challenge of establishing processes for expanding $V\delta1^+$ γδ T-cells from the very low numbers of cells present in the blood (Nussbaumer and Koslowski 2019). The sponsor has developed a proprietary expansion method for $V\delta1^+$ γδ T-cells derived from the leukapheresis material of a healthy donor.

Gamma delta T-cells represent an evolutionarily highly conserved lymphocyte subset with unique properties that enable them to combine the specificity of an adaptive immune response with the speed of an innate cellular response. Gamma delta T-cells can be classified through their usage of 8 different delta chain variable genes (Vδ1-Vδ8) to rearrange their T-cell receptor (TCR). The 2 main subsets of γδ T-cells are variable delta 1 chain ($V\delta1^+$) and variable delta 2 chain ($V\delta2^+$) T-cells. Vδ2 T-cells constitute the major population (>70%) of peripheral blood γδ T-cells and up to 10% of T-cells within peripheral blood mononuclear cells (PBMCs) in healthy individuals. These invariant T-cells respond to metabolites produced by bacteria and protozoa and can rapidly expand in response to infections (Nussbaumer and Koslowski 2019).

Variable $\delta1^+$ γδ T-cells, in contrast, are predominantly tissue resident T-cells and dominate the γδ T-cell repertoire in epithelial tissues while populating the blood of healthy individuals only in low numbers. Within tissues and blood, they recognize and target transformed or diseased cells via direct ligand recognition through cell surface, activating receptors such as NKG2D and natural cytotoxicity receptors (NCRs) (Hayday 2009) (Hannani et al. 2012; Vantourout and Hayday 2013). Independent of the TCR, this tumor cell recognition is not clonally restricted, and $V\delta1^+$ γδ T-cells become activated following receptor binding to cognate ligands on malignant cells. Activation leads to the secretion of cytokines, eg, IFNγ and tumor necrosis factor alpha (TNFα), which can induce tumor cell cycle arrest, and to the release of cytotoxic granules such as perforin and granzymes that disrupt the target cell membrane, inducing tumor cell death (Silva-Santos et al. 2019). Importantly, $V\delta1^+$ γδ T-cell target cell recognition is not MHC-restricted and γδ T-cells are not allogeneic human leukocyte antigen (HLA) reactive, thus allowing for a potent graft versus leukemia effect while minimizing the risk of graft versus host disease (GvHD) when applied as allogeneic therapy (Godder et al. 2007) (Minculescu et al. 2019).

4.1.3 Nonclinical Experience

Nonclinical studies have been conducted to demonstrate the antitumor activity and address potential risks associated with GDX012. Nonclinical studies focused on in vitro assessment of

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GDX012 activity and safety, supported by in vivo studies to assess the antitumor efficacy and tolerability of GDX012 in immune-compromised mouse xenograft models.

[redacted]

In vitro nonclinical safety studies were conducted to assess the potential for tumorigenicity, immunogenicity, and off-target activities of GDX012. These studies demonstrated the following:

- GDX012 has a high degree of TCR polyclonality and diversity supportive of a low risk of tumorigenicity.
- GDX012 shows a Th1 cytokine release profile following stimulation; cytokines associated with CRS are either not detected (eg, interleukin [IL]-2, IL-6,) or detected at very low levels that are well within the normal physiological range (eg, TNFα, IFNγ).
- GDX012 does not stimulate other immune cells to produce significant quantities of the CRS-related cytokines IL-6 or TNFα.
- GDX012 cytotoxic activity is highly selective for transformed cells and does not mediate off-target toxicities.
- GDX012 is not alloreactive and does not show activation in mixed lymphocyte reactions.

Nonclinical study results and detailed nonclinical study information are provided in the GDX012 Investigator's Brochure.

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4.1.4 Clinical Experience

A first-in-human (FIH) study (GDX012U-001) was initiated to assess the safety, tolerability and preliminary antileukemic activity of GDX012 in patients with measurable residual disease (MRD) positive AML in July 2021. The study was prematurely discontinued due to a business decision and not related to the safety of the GDX012. [redacted] which was well tolerated with only 2 Grade 1 events reported.

- No DLTs, treatment-emergent adverse events (TEAEs) leading to death or treatment discontinuation nor TEAEs related to CRS or GvHD were reported.

Further information is provided in the GDX012 Investigator's Brochure.

4.1.5 Known and Potential Benefits and Risks to Patients

Preclinical evidence demonstrates that GDX012 is cytotoxic against leukemic blasts, is able to infiltrate the bone marrow and Vδ1 γδ T-cells are able to significantly reduce the in vivo tumor burden in myeloid leukemia and other hematologic malignant models (Almeida et al. 2016) (Di

Lorenzo et al. 2019). Furthermore, clinical data indicates a high recovery of Vδ1 γδ T-cells following hematopoietic stem cell transplantation (HSCT) enhances overall survival and relapse-free survival in patients with hematological malignancies including AML (Airoldi et al. 2015) (Godder et al. 2007), (Minculescu et al. 2019). Patients receiving αβ T-cell depleted haploidentical bone marrow transplants which are enriched in δγ T-cells demonstrated better leukemia free survival than other mismatched donors and no Grade 3-4 GvHD (Bertaina et al. 2018).

Clinical data for GDX012 from the FIH study is limited to date, the clinical data along with data from nonclinical studies demonstrate a safety and activity profile that supports the therapeutic potential for Vδ1 γδ T-cells in patients with R/R AML who have very limited therapeutic options and therefore, there is a reasonable risk/benefit.

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 (Table 4.a). GDX012 is expected to have a lower toxicity profile than therapies utilizing αβ T-cells, but toxicities may still occur.

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Table 4.a Potential Risks of GDX012

Potential Risk	Rationale for Risk	Mitigation
GvHD	GDX012 is an allogeneic product which is not HLA matched. In clinical studies of HSCT degree of allogeneic mismatch impacts GvHD. However, γδ T-cells are not allogeneic HLA reactive.	The risk is expected to be low due to the biology of γδ T-cells. The contribution of αβ T-cells in the product is limited to <50,000 cells/kg. Awareness of this risk by healthcare providers allows for monitoring for signs and symptoms.
Infection	GDX012 is preceded by conditioning chemotherapy which can cause short term suppression of the immune system through development of leukopenia. It is not known whether GDX012 can contribute to these cytopenias.	Prophylactic anti-infective therapies are recommended per institutional guidelines. GDX012 is expected to spare healthy cells and not add additional toxicity.
Hypersensitivity Reactions	Hypersensitivity reactions have been observed in allogeneic and autologous cell products. One mild reaction was observed in a patient previously treated with GDX012.	Prophylactic treatments to prevent hypersensitivity reaction are given before infusion. Awareness of this risk by health care providers allows for monitoring and early intervention.
CRS/ICANS	CRS/ICANS has been observed in CAR T-cell and other targeted immunotherapy studies. However, cytokine release syndrome and ICANS are not anticipated with GDX012 since these toxicities have not been reported in transplant studies with high numbers of $V\delta1^+$ γδ T-cells, clinical trials with $V\delta1^+$ γδ T-cells, Vδ2+ γδ T-cells or unmodified αβ T-cells such	Nonclinical studies of GDX012 show limited production of Th1 cytokines upon stimulation so the risk of CRS is considered to be low. Patients with active CNS disease or neurologic medical history are excluded. Pharmacologic intervention strategies are provided.

Table 4.a Potential Risks of GDX012

Potential Risk	Rationale for Risk	Mitigation
	as TILs or donor lymphocyte infusions.	
Bone marrow suppression	Prolonged cytopenias have been reported in CAR T-cell studies. Preclinical models and clinical trials of CAR T-cells targeted at AML have demonstrated significant toxicity to HSCs.	GDX012 is an unmodified cell therapy so off tumor toxicity from targeting cell surface antigens expressed on tumor and HSCs is not expected. Supportive care measures including G-CSF and transfusion support are allowed.

AML: acute myeloid leukemia; CAR: chimeric antigen receptor; CNS: central nervous system; CRS: cytokine release syndrome; G-CSF: granulocyte colony stimulating factor; GvHD: graft-versus-host disease; HLA: human leukocyte antigen; HSC: hematopoietic stem cell; HSCT: hematopoietic stem cell transplantation; ICANS: immune effector cell-associated neurotoxicity syndrome; Th1: T helper 1.

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4.2 Rationale for the Proposed Study

Rationale for GDX012 in AML

The benefit of immune and cell based therapy for leukemia in general, and AML specifically has been demonstrated by the successful use of hematopoeitc stem cell transplant as a potentially curative therapy (Dickinson et al. 2017). The benefit of stem cell transplantation relies not just on the antitumor effect of high dose therapy but on the so called "graft-vs-leukemia" effect that occurs when T-cells from the graft recognize and kill residual leukemia (Mardiana and Gill 2020). Immunotherapies such as CAR T-cells have sought to harness this immune based killing, and while progress has been made with B-cell malignancies, lack of a leukemia specific target has been limiting for AML. Vδ1 γδ T-cells represent a potential immune based approach which may not be limited in this way. Due to the ability to recognize and respond to tumor cells without modification to recognize a cell surface target and the lack of major histocompatibility complex (MHC) restriction and HLA reactivity, Vδ1 γδ T-cells have the potential for graft-versus-leukemia effect while minimizing the risk of GvHD when applied as allogeneic therapy (Godder et al. 2007) (Minculescu et al. 2019).

The therapeutic potential of human Vδ1 γδ T-cells for the treatment of hematologic malignancies is supported by preclinical data that show strong and broad antileukemic activity of $V\delta1^{+}$ γδ T-cells in vitro and in vivo (Almeida et al. 2016) (Di Lorenzo et al. 2019). Furthermore, numerous clinical studies have shown the reconstitution of a high number of Vδ1 γδ T-cells early after allogeneic and autologous stem cell transplantation in patients with hematological malignancies correlate with improved OS and relapse-free survival and a lower incidence of GvHD (Godder et al. 2007) (Airoldi et al. 2015; Minculescu et al. 2019).

Analysis of the biodistribution of GDX012 in vivo in a murine xenograft model further supports the clinical application of GDX012 in the treatment of myeloid malignancies. When administered systemically in this model, GDX012 can be detected in the bone marrow at least 28 days after a

single dose, suggesting that GDX012 has the capacity to home to and infiltrate the bone marrow during this period of observation.

Rationale for Study Population

The population of this study will include patients with relapsed or refractory AML and in phase 1, it will include patients who are not candidates for HSCT. This population has limited treatment options and poor survival. As such, these patients benefit from the ability to enroll in clinical trials. Further, since most of the patients in phase 1 will not progress to HSCT if CR is achieved, the safety parameters and clinical pharmacology of the cell product can be established over a longer time period since transplantation would likely eliminate the Vδ1 γδ T-cells.

Rationale for Study Design

This is a phase 1/2a open-label dose escalation and dose expansion study. The purpose of this study is to establish the safety, tolerability, and recommended phase 2 dose (RP2D) for future studies of GDX012. The study employs an open-label dose escalation to establish maximum tolerated dose (MTD) followed by an expansion of 1 dose or randomization to 2 dose cohorts in which both safety and response data are considered. The Bayesian optimal interval (BOIN) design and interim analysis for futility assessment aim to limit exposure to subtherapeutic or potentially toxic doses. In both phase 1 and 2a, the primary and secondary outcome measures are assessed at 30 days post dose (dose-limiting toxicity [DLT] period). This represents both the standard of care for disease assessment in AML as well as any acute toxicities that may potentially occur. A primary follow-up period of 100 days allows for further safety assessment for potential GvHD.

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4.2.1 Rationale for Dose Selection, Regimen, and Modification

Since GDX012 has not had sufficient administration to humans to establish safe dosing, dose selection is based upon clinical experience from haploidentical hematopoietic stem cell transplantation (haplo-HSCT) and studies with similar T-cell products (tumor-infiltrating lymphocytes [TILs] and Vδ2 γδ T-cells).

Adoptive transfer of autologous TILs has shown that Vδ1 γδ T-cells can represent the major TIL subset, accounting for up to 50% of the total $CD3^+$ population (Cordova et al. 2012). Detectable amounts of Vδ1 γδ T-cells in clinical grade TIL preparations were found in 20 of 27 patients in an adoptive TIL transfer study, and infusion products from 10 patients contained, on average, greater than 1×10^9 and up to 6.5×10^9 Vδ1 γδ T-cells. Infusions were safe and well tolerated (Donia et al. 2012). Our proposed starting dose [redacted] is similar to the average and approximately 8-fold lower than the highest Vδ1 γδ T-cell numbers detected in adoptive transfer of TILs. In a previous study of GDX 012 in patients with MRD^+ AML, 3 patients were treated at a dose of [redacted] without DLTs before sponsor discontinuation of the study for non-safety reasons. The proposed starting dose would have been the next dose evaluated had that study continued to enroll. Additional dose levels are selected to give sufficient separation to allow for differences in safety outcomes to be assessed. The 3 dose levels of GDX012 are detailed in Table 4.b.

Table 4.b Dose Escalation Plan

[redacted]

Since GDX012 is an allogeneic product, it is potentially susceptible to rejection by host immune cells. The duration of persistence of GDX012 is not known, but it may not be sufficient to completely irradicate AML in a single dose. Patients who are demonstrating potential benefit from treatment (ie, patients who achieve a response including CR, CRh, CRi, MLFS, or PR based on 2022 European LeukemiaNet [ELN] response criteria for AML) may receive a second dose (at the same dose level) at the investigator's discretion. A second dose will be preceded by a de-intensified lymphodepleting chemotherapy regimen and will follow the same assessment schedule as the initial dose. Since GDX012 contains some αβ T-cells, the lymphodepletion before the second dose will serve to support both expansion of GDX012 and eradicate any previously administered αβ T-cells so that the exposure at any given time is not increased by the administration of a second dose. For patients who continue on to a second dose, no more than 30 days may elapse between completion of disease evaluation and start of lymphodepletion. Details are described in Section 6.1.2.

All doses of GDX012 will be preceded by lymphodepleting chemotherapy. It has been demonstrated in multiple studies of ACTs that conditioning chemotherapy enhances the expansion and activity of these therapies. The most commonly utilized agents are [redacted] which will be utilized in this study.

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objective

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

5.1.3 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.

5.2 Estimands

Not Applicable.

5.3 Endpoints

5.3.1 Primary Endpoints

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

5.3.2 Secondary Endpoints

- 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.

5.3.3 Exploratory Endpoints

- 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.

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- 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 (Appendix D).

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6.0 STUDY DESIGN

6.1 Overview of 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 R/R AML. The results of this study are intended to enable and inform the design of subsequent studies using GDX012 in this and other indications. The overall outcome of the study will be based on totality of the evidence, including the phase 1 and 2a study designs outlined below, as well as the CK (expansion and persistence) of GDX012 and pharmacodynamic activity from blood and bone marrow data available.

During phase 1, cohorts of 3 to 6 patients will receive escalating doses of GDX012 in 3 dose levels (see Table 4.b) following the BOIN design. Upon completion of phase 1, 1 to 2 dose levels will be selected for phase 2a of the study. 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 infusion. 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.

For both phases of the study, patients with R/R AML will be asked to sign the study informed consent form (ICF) before undergoing screening for the study. Patients who sign the ICF and meet the protocol defined eligibility criteria following screening will be enrolled. Patients who do not meet the protocol defined eligibility criteria will be screen failures.

Screening assessments must be performed within 21 days of starting lymphodepleting chemotherapy (Day -5).

Eligible patients will undergo lymphodepleting chemotherapy with [redacted] 30 mg/m^2/day IV for 3 days (Day -5 to Day -3) and [redacted] 500 mg/m^2/day IV for 3 days (Day -5 to Day -3) followed by infusion of GDX012 on Day 1.

During phase 1, patients will be hospitalized for observation for at least 3 days after GDX012 infusion and may subsequently be discharged at the investigator's discretion. If no acute toxicities are observed during phase 1, patients in phase 2a may be discharged at the investigator's discretion following the GDX012 infusion.

Patients will have the following study visits for assessment of eligibility, safety, efficacy, CK, and biomarkers: screening, lymphodepleting chemotherapy (Days -5 to -3), GDX012 infusion (Day 1), immediate post infusion monitoring (Day 2 through Day 4), and post-infusion assessments on Days 5, 8, 11, 14, 17, 21, 30, 60, and 100. Patients who do not recover blood counts by Day 30 will undergo a repeat bone marrow evaluation at Day 45. The window for evaluating patients for DLTs will be 30 days following infusion of GDX012, however, patients who have myelosuppression at Day 30 which recovers by Day 45 will not be considered to have a DLT.

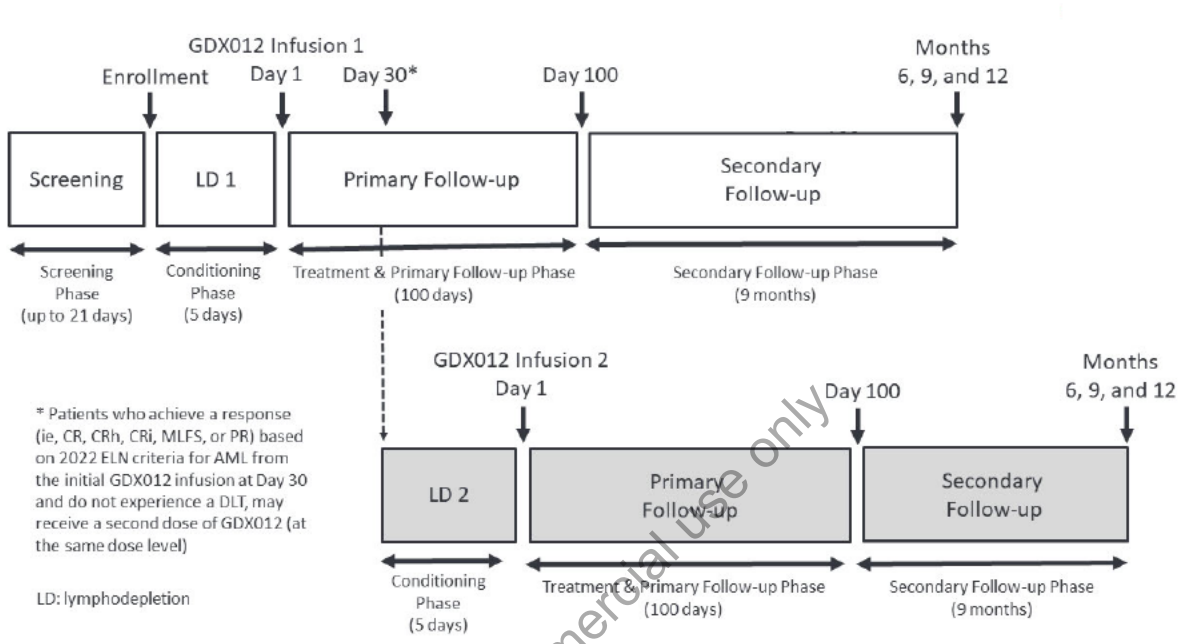
The clinical cutoff to evaluate safety will occur once all patients have been followed for at least 100 days after last GDX012 infusion (or died or withdrawn from the study). After the Day 100 assessments, patients will continue to be followed at 6, 9, and 12 months after last GDX012 infusion (Figure 6.a).

Patients who achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on 2022 ELN response criteria for AML from the initial GDX012 infusion at Day 30, do not experience a DLT, and are healthy enough to undergo a second lymphodepletion may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion. Second doses will be preceded by a de-intensified lymphodepleting chemotherapy regimen and will follow the same assessment schedule as the initial dose. For patients who continue on to a second dose, no more than 30 days may elapse between completion of disease evaluation and start of lymphodepletion.

The overall study schema for GDX012-1501 is illustrated in Figure 6.a.

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Figure 6.a Study Schematic for TAK-012-1501 Protocol



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An exploratory cohort(s) may be enrolled to explore an alternative conditioning regimen or dose schema after completion of phase 1. These cohort(s) will enroll approximately 10 to 20 patients and be implemented via a protocol amendment.

6.1.1 Phase 1 Study Design

Dose escalation of GDX012 will follow BOIN design (Liu and Yuan 2015) (Yuan et al. 2016) 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.a and detailed in Appendix E, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation. Overdose control is implemented to eliminate certain dose levels from from further examination.

Table 6.a 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.

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.

6.1.1.1 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.

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6.1.2 Phase 2a Study Design

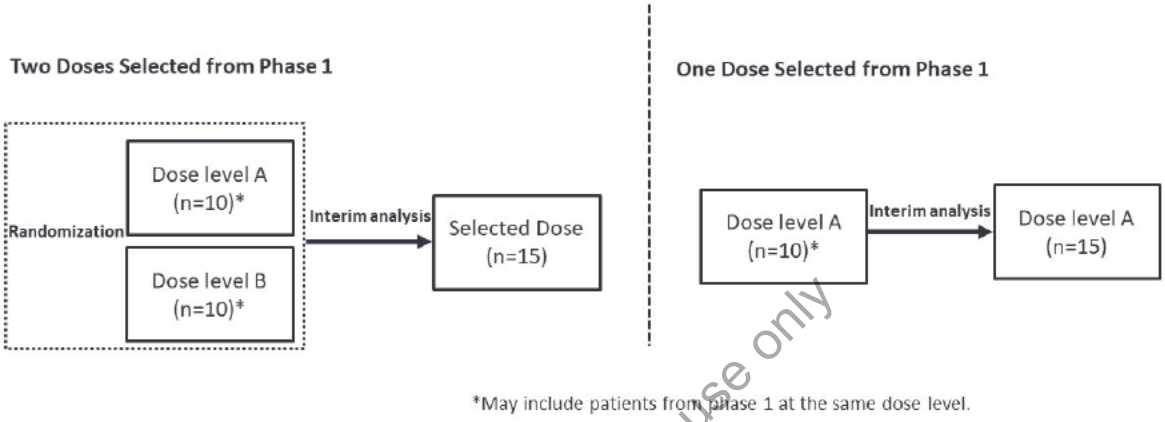
Dose expansion cohorts will be monitored using the Bayesian optimal phase 2 (BOP2) design (Zhou et al. 2017).

- 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 (Figure 6.b). 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 infusion. 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 stopping boundaries at futility and final analysis are generated through optimization using uninteresting response (ie, CR, CRh, or CRi after last dose) rate 30% and target response rate 50% with one-sided type I error rate 10%. Specifically, the enrolment may not be continued if there are less than or equal to 2 CR,CRi, or CRh among the first 10 response-evaluable patients at each dose level.

The patients in expansion cohorts may include patients from dose escalation phase treated with same dose level.

Figure 6.b Schematic of Phase 2a Study Design



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6.2 Number of Patients

The expected total number of patients to be enrolled in the study is approximately 53, of which approximately 18 DLT-evaluable patients will be enrolled in phase 1, and approximately 35 patients will be enrolled in phase 2a of the study. Approximately 15 study sites across the United States will participate in this study. In addition, 1 or more exploratory cohorts may be enrolled at a future date. Approximately 10 to 20 patients will be included in these cohorts.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients who receive a single administration of GDX012 will be followed for 12 months after GDX012 administration. Including screening duration, participation for these patients will be approximately 13 months. Patients who receive a second dose of GDX012 will be followed for approximately 12 months after the last administration. Including screening duration, participation for these patients will be approximately 15 months.

6.3.2 EOS/Study Completion Definition and Planned Reporting

The primary analysis for the primary and secondary endpoints will be conducted and documented in a CSR after all dosed patients in the study have had the opportunity to be assessed for safety at least 100-days after last GDX012 infusion. The data cutoff for final analysis for the CSR will be conducted after all patients have have been followed for 12 months after their last dose of GDX012, death, or withdrawal from the study. The current study will be considered complete after the final analysis has been completed or the study has been terminated by the sponsor. EOS is defined as either the date of the last visit of the last patient, the date of the last follow-up, or the receipt of the last data point from the last patient that is required for at least primary and secondary analyses, as prespecified in the protocol, whichever is the later date.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.b for disclosures information for all primary and secondary endpoints.

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Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary Endpoint:		
Incidence of DLTs, MTD	Incidence of toxicities defined in the protocol as DLTs	Up to 1 month
Incidence of TEAEs, including SAEs and clinically significant laboratory values		Up to 12 months
Secondary Endpoints:		
Disease response per investigator	Including CR, CRh, CRi, MLFS, and PR at Day 30 after last dose of GDX012	Up to 14 months
MRD	MRD by flow cytometry. MRD negative state defined by <0.1% detectable disease based on local assessment of bone marrow	Up to 14 months
DOR	Only for patients who experience a response of CR, CRh, or CRi and is the time from the date of establishment of response to disease progression (Appendix F) or death, whichever comes first	Up to 14 months
EFS	Time from first dose to not achieving response, relapse, or death	Up to 14 months
OS	Time from first dose to the date of death from any cause	Up to 14 months

CR: complete response; CRh: complete response with partial hematologic recovery; CRi: complete response with incomplete hematologic recovery; DOR: duration of response; DLT: dose-limiting toxicity; EFS: event-free survival; MLFS: morphological leukemia-free state; MRD: measurable residual disease; OS: overall survival; PR: partial response; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

6.3.4 Total Study Duration

The estimated time frame for study completion is 3.5 to 4 years, including approximately 30 months for enrollment and a 12-month follow-up after the last patient is dosed.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Aged ≥18 years at the time of signing the informed consent.
2. Total body weight of ≥40 kg.
3. Must have pathologically confirmed R/R AML per 2022 International Consensus Classification (ICC) classification, as follows:
   a. Relapsed AML is defined as the appearance of ≥5% blasts in the BM or peripheral blood at any time after achieving a CR, CRh, CRi, or MLFS.
   b. Refractory AML is defined as failure to achieve a CR, CRh, CRi, or MLFS after 1 of the following regimens:
      i. Two courses of intensive induction chemotherapy, eg, 7+3 (7 days of cytarabine plus 3 days of anthracycline); mitoxantrone, etoposide, and cytarabine; high-dose cytarabine; etc. (where 5+2 given on Days 14 to 21 for persistent leukemia on Day 14 will count as a second induction or 1 induction attempt is required for patients >60 years of age.
      ii. At least 2 cycles of hypomethylating agent (HMA) or low-dose, cytarabine-based combination regimen including, but not limited to, venetoclax or other B-cell lymphoma 2 (BCL2) inhibitors.
      iii. At least 4 cycles of HMA monotherapy.
4. During dose escalation, patients must be ineligible for HSCT due to comorbid condition, inability to receive HSCT conditioning, lack of an available donor, patient having declined procedure after documented discussion of the risks and benefits, or investigator considers it not to be in the best interest of the patient.
5. Must have an anticipated life expectancy of >3 months before lymphodepletion.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix G).
7. Left ventricular ejection fraction of ≥40% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan.

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8. Adequate organ function as indicated by the laboratory values below:

System	Laboratory Value
Coagulation:	
• Platelet count	• $\geq 30 \times 10^9$/L (transfusion allowed)
• Prothrombin time or international normalized ratio	• ≤1.5 × upper limit of normal (ULN) unless receiving therapeutic or prophylactic anticoagulation
• Partial thromboplastin time	• ≤1.5 × ULN unless receiving therapeutic or prophylactic anticoagulation
Hematology:	
• Hemoglobin	• ≥7.0 g/dL (transfusion allowed)
Renal:	
• Calculated or measured creatinine clearance [a]	• ≥30 mL/min
Hepatic:	
• Serum total bilirubin	• ≤1.5 × ULN (higher levels are acceptable if these can be attributed to active hemolysis (as indicated by positive Coomb's test result, decreased haptoglobin, documented Gilbert's disease, elevated indirect bilirubin, and/or lactate dehydrogenase) or ineffective erythropoiesis (as indicated by bone marrow findings)
• Alanine aminotransferase (ALT)	• ≤2.5 × ULN
• Aspartate aminotransferase (AST)	• ≤2.5 × ULN

a. Renal function (creatinine clearance or surrogate glomerular filtration rate) will be estimated or measured according to standard practice at the treating institution.

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9. Female patients who:
   a. Are postmenopausal for at least 1 year before the screening visit, or
   b. Are surgically sterile, or
   c. If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through at least 12 months following GDX012 administration, or
   d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and

e. Agree not to breastfeed a baby or donate an egg or eggs (ova) during the study and until at least 12 months following GDX012 administration.

10. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    a. Agree to practice effective barrier contraception from the time of signing the informed consent through at least 12 months following GDX012 administration, or
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and
    c. Agree not to donate sperm during the study and at least until 12 months following GDX012 administration.
11. Voluntary written consent before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Willingness and ability to comply with scheduled visits and study procedures.

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7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Diagnosis of acute promyelocytic leukemia.
2. Has received or plans to receive any of the following excluded therapy/treatment within the specified timeframe before lymphodepleting chemotherapy:
    a. Cytotoxic chemotherapy or immunotherapy within 2 weeks before lymphodepletion. Hydroxyurea is allowed up to 2 days before start of lymphodepletion. Intrathecal chemotherapy is allowed up to 7 days before lymphodepletion. Hypomethylating agents are allowed up to 10 days before lymphodepletion.
    b. Corticosteroids or any other immunosuppressive therapy within 2 weeks before lymphodepletion, with exception of the following:
        i. Use of inhaled, topical, intranasal, ocular, or intra articular corticosteroids.
        ii. Physiological doses of replacement steroids (eg, for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent.
    c. Investigational treatment or interventional clinical trial within 2 weeks or 5 half lives (if known), whichever is longer, before lymphodepletion.
    d. Major surgery within 4 weeks before lymphodepletion (patients must have fully recovered from any surgery related toxicities).
    e. Donor lymphocyte infusion within 30 days before lymphodepletion for patients who have previously undergone HSCT.

3. Prior allogeneic HSCT within 3 months of signing ICF or with ongoing requirement for systemic graft-versus-host therapy.
4. Has received prior gene or modified cell therapy (eg, CAR-T or CAR-NK).
5. WBC >20,000/μL or evidence of rapid disease progression that would prevent completion of at least 1 dose cycle. (Cytoreductive therapies including leukapheresis or hydroxyurea are allowed.)
6. Ongoing nonhematologic toxicity from prior anticancer therapy that has not recovered to Grade ≤1 before enrollment (except for nonclinically significant toxicities, eg, alopecia, vitiligo), with the exception of patients with Grade 2 toxicities that are deemed stable or irreversible (eg, hypothyroidism), who may be enrolled at the investigator's discretion.
7. Known hypersensitivity to [redacted], or other agents, or excipients used in the study.
8. History of chronic or recurrent (within the last year before screening) severe autoimmune or immune-mediated disease requiring steroids or other immunosuppressive treatments, including antitumor necrosis factor agents.
9. Active central nervous system involvement (eg, symptomatic, central nervous system [CNS] 3, or radiologically detected disease). Patients with history of CNS leukemia which has been adequately treated will be considered eligible.
10. History or presence of active/clinically relevant CNS disorder such as seizure, encephalopathy, cerebrovascular ischemia/hemorrhage, severe dementia, cerebellar disease, or any autoimmune disease with CNS involvement. For CNS disorders that recover or are in remission, patients without recurrence within 2 years of planned study enrollment may be included.
11. History of malignancy are excluded with the following exceptions:
    a. Patients with a history of treated, non-melanoma skin cancer, or in situ carcinoma of cervix, bladder, or breast who have received curative treatment anytime before screening.
    b. Patients with low-grade, early stage prostate cancer (eg, Gleason score ≤6, stage 1 or 2) with no requirement for therapy anytime prior to enrollment.
    c. Any other malignancy status post curative intent therapy and in remission without treatment for ≥2 years before enrollment.
    d. Patients on adjuvant endocrine therapy for localized hormone receptor positive breast cancer for ≥2 years before enrollment.

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12. Uncontrolled intercurrent illness including, but not limited to, the following:
    a. Ongoing or active infection (eg, requiring systemic antimicrobial therapy for treatment of infection within 5 days before start of lymphodepletion). Patients on long-term antimicrobial therapy with no evidence of active disease and those on prophylactic antimicrobials are not excluded.
    b. Clinically significant cardiac disease defined by congestive heart failure New York Heart Association Class 3 or Class 4.
    c. Clinically significant (symptomatic) cardiac arrhythmias (eg, sustained ventricular tachycardia, second- or third-degree atrioventricular block without a pacemaker, or circulatory collapse arrhythmia requiring therapy).
    d. Acute coronary syndrome (unstable angina or myocardial infarction) in the last 6 months. Patients with medically controlled angina may be enrolled.
    e. Interstitial lung disease causing them to be oxygen dependent.
13. Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) as defined below:
    a. Positive serology for HIV.
    b. Positive hepatitis B surface antigen (HBsAg) test and/or positive HBV deoxyribonucleic acid (DNA) test. Patients who are HBsAg negative but are hepatitis B core antibody positive must have undetectable HBV DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated before lymphodepleting therapy and continued for 6 months.
    c. Positive HCV RNA test. Patients who are hepatitis C antibody positive will be screened for HCV RNA by any reverse transcription PCR or branched DNA assay. If hepatitis C antibody is positive, eligibility will be determined based on a negative screening RNA value.
14. Clinically active severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) viral infection defined by prior positive test or presumptive symptoms without demonstration of a negative test.
15. Female patients who are lactating and breastfeeding.
16. Female patients who have a positive serum pregnancy test.
17. Any other medical, psychological, or social condition that, in the opinion of the principal investigator (PI), would contraindicate the patient's participation in the clinical study due to safety or compliance with clinical study procedures.

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8.0 STUDY DRUG

GDX012 suspension for IV infusion (referred to as GDX012) is a novel allogeneic cell therapy that is enriched for Vδ1$^+$ γδ T-cells. [redacted]

Patients must meet all inclusion and exclusion criteria before initiation of lymphodepleting chemotherapy. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

If an enrolled patient becomes ineligible to receive GDX012 administration due to development of medical complications, such as systemic infection, sepsis, hemodynamic instability, or altered mental status during/immediately after lymphodepleting chemotherapy but before GDX012 administration, GDX012 administration may be delayed for up to 7 days on investigator's decision. The investigator is required to consult with the sponsor medical monitor in case of delayed GDX012 administration.

The first GDX012 administration will follow lymphodepleting chemotherapy ([redacted] 30 mg/m^2 body surface area [BSA] per day IV on Days -5, -4, and -3 and [redacted] 500 mg/m^2 BSA per day IV on Days -5, -4, and -3). At least 2 days must elapse between the end of lymphodepleting chemotherapy and GDX012 administration. Day 1 will be defined as the actual day of GDX012 administration.

Patients who achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on ELN 2022 response criteria from the initial GDX012 infusion at Day 30, do not experience a DLT, and are healthy enough to undergo a second lymphodepletion may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion. Second doses will be preceded by a de-intensified lymphodepleting chemotherapy regimen ([redacted] 25 mg/m^2 BSA/day IV on Days -5, -4, and -3 and [redacted] 300 mg/m^2 BSA/day IV on Days -5, -4, and -3) and will follow the same assessment schedule as the initial dose. For patients who continue on to a second dose, no more than 30 days may elapse between completion of disease evaluation and start of lymphodepletion.

The instructions for administration of lymphodepleting chemotherapy are outlined in the cell handling manual. Details for handling (eg, shipping, receipt, thaw) and administration of GDX012 are contained in the cell handling manual.

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8.2 Prohibited Concomitant Medications and Procedures

The following medications are prohibited within the specified timeframe before lymphodepleting chemotherapy through primary follow-up phase (100 days after GDX012 administration) for phase 1 and through completion of first disease assessment for phase 2a:

- Cytotoxic chemotherapy or immunotherapy within 2 weeks before lymphodepletion. Hydroxyurea is allowed up to 2 days before start of lymphodepletion. Intrathecal chemotherapy is allowed up to 7 days before lymphodepletion. Hypomethylating agents are allowed up to 10 days prior to lymphodepletion.
- Corticosteroids or any other immunosuppressive therapy within 2 weeks before lymphodepletion, with exception of the following:
  - Use of inhaled, topical, intranasal, ocular, or intra articular corticosteroids.
  - Physiological doses of replacement steroids (eg, for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent.
- Investigational treatment or interventional clinical trial within 2 weeks or 5 half lives (if known), whichever is longer, before lymphodepletion.
- Major surgery within 4 weeks before lymphodepletion (patients must have fully recovered from any surgery related toxicities).
- Donor lymphocyte infusion within 30 days before lymphodepletion for patients who have previously undergone HSCT.
- Prior allogeneic HSCT within 3 months of signing ICF or with ongoing requirement for systemic graft-versus-host therapy.
- Granulocyte macrophage colony-stimulating factors 14 days after GDX012 administration.
- Live vaccines and vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza are permitted.

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Patients may receive these medications/procedures if deemed necessary for their welfare; however, the investigator, medical monitor, and/or Sponsor must review all patients receiving prohibited medications/procedures and may decide to withdraw these patients from the study based on the best interests of the patient or to allow replacement to ensure the minimum number of evaluable patients complete the DLT period.

8.3 Permitted Concomitant Medications and Procedures

Supportive treatment and premedication, per investigator's discretion and/or institutional guidelines for management of patients receiving lymphodepleting conditioning and GDX012, except the prohibited concomitant medications, is allowed. The patient must be told to notify the investigational site about any new medications taken after GDX012 administration. Bacterial, fungal, viral prophylaxis, and appropriate management of infections and antibiotics are allowed as

needed per investigator's discretion and/or institutional guidelines. In addition, supportive care measures (eg, use of antiemetics and antimotility agents for diarrhea management) are permitted at the investigator's discretion and/or per institutional guidelines. For patients with neutropenia beyond 14 days after infusion, G-CSF is encouraged.

All medications and significant nondrug therapies (including physical therapy, herbal/natural medications, and blood products) administered during the study must be listed on the Concomitant Medications, Surgeries, and Procedures case report forms (CRFs). Any prior medication received up to 28 days before the administration of lymphodepleting chemotherapy will also be recorded in the appropriate CRF. Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without consultation with the investigator.

8.4 Precautions and Restrictions

Appropriate safety measures should be taken when treating patients with GDX012.

Cytokine release syndrome and ICANS are not anticipated with GDX012 since these toxicities have not been reported in transplant studies with high numbers of $V\delta1^+$ γδ T-cells, clinical trials with $V\delta1^+$ γδ T-cells, $V\delta2^+$ γδ T-cells or unmodified αβ T-cells such as TILs or donor lymphocyte infusions. The risk of CRS and ICANS are low because these unmodified cells are subject to endogenous regulation and are not expected to undergo extensive expansion or supraphysiological activation. However, as a precautionary measure, all patients will be assessesed. Assessment and grading of CRS and ICANS will be performed following the definition provided in the American Society for Transplantation and Cellular Therapy (ASTCT) consensus (Lee et al. 2019) [Appendix H and Appendix I]. Toxicity management will follow the recommendation of the CARTOX (CAR T–cell therapy–associated TOXicity) Working Group (Appendix J) or be performed according to institutional guidelines. Other recommended mitigation strategies for each of the potential risks are provided in Section 8.5.

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The potential risk of GvHD is expected to be low. Unlike αβ T-cells, γδ T-cells do not recognize HLA so it is not expected that HLA disparity between host and GDX012 donor will induce GvHD. Further, residual αβ T-cells in the GDX012 infusion is limited to <50,000 cells/kg patient weight, a dose which has been studied in other allogeneic therapies to have limited potential to cause GvHD. Long-term engraftment of allogeneic T-cells is not expected further limiting this risk.

For patients experiencing GvHD, management and treatment should be provided as detailed in Section 8.5.

Acute or delayed infusion-related reactions (IRRs) may occur with any IV-administered investigational product. Patients must be monitored during GDX012 administration for any acute reaction.

Infusion-related reactions may manifest as localized infusion site reactions or systemic IRRs and may include (but not limited to) symptoms such as rash, erythema, pruritus, fever or chills, or anaphylactic-type reaction.

If there are early signs of IRR during the GDX012 infusion, the investigator may interrupt the infusion in order to assess the patient. If symptoms resolve without treatment or respond to treatment with antihistamines, antipyretics, and fluids, and are considered by the investigator to be of no safety risk to the patient, the GDX012 infusion may be resumed. For Grade ≥3 IRRs, the infusion must be stopped, and the patient's reaction discussed with the Sponsor or designee (medical monitor).

Should any IRRs occur during the observation period after completion of the infusion, symptoms should be treated according to standard clinical care measures at the discretion of the investigator.

It is not known what effects GDX012 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner for 1 year after the dose of GDX012. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following (see Appendix K):

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 1 year after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and
- Agree not to breastfeed a baby or donate an egg or eggs (ova) during the study and until at least 12 months following GDX012 administration.

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception from the time of signing of the informed consent through 1 year after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception). Female and male condoms should not be used together, and
- Agree not to donate sperm during the study and at least 12 months following GDX012 administration.

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Before starting treatment, male patients should be advised to seek counseling on sperm storage, and female patients should be advised to seek counseling on egg storage.

8.5 Management and Mitigation of AEs

Investigators should use clinical judgement and refer to the following treatment Guidelines on Toxicity Assessment and Management as needed (Table 8.a).

Table 8.a Toxicity Assessment and Management Guidelines

Toxicity	Monitoring, Assessment, and Management Guidelines
CRS	• Close monitoring of patients during and after GDX012 administration according to the study protocol. • Grading will follow ASTCT Consensus Grading for CRS and Neurologic Toxicity Associated with Immune Effector Cells. • Toxicity management will follow Immune Effector Cell Therapy Toxicity Assessment and Management (also known as CARTOX).
ICANS	• Close monitoring of patients after GDX012 administration according to the study protocol. • Grading will follow ASTCT Consensus Grading for CRS and Neurologic Toxicity Associated with Immune Effector Cells. • Toxicity management will follow Immune Effector Cell Therapy Toxicity Assessment and Management (also known as CARTOX).
GvHD	• Close monitoring of patients after GDX012 administration according to the study protocol. • Grading for acute cell therapy associated GvHD will follow Mount Sinai Acute GvHD International Consortium grading for acute cell-therapy associated GvHD. • Grading for chronic cell therapy associated GvHD will follow 2014 National Institutes of Health Consensus Conference grading for chronic cell therapy associated GvHD. • Toxicity management will follow local guidelines and practice.
TLS	• Close monitoring of patients after GDX012 administration according to study protocol. • Grading will follow Cairo-Bishop grading of clinical TLS for adults. • Toxicity management as per local guidelines and practice
Hypersensitivity and IRRs	• Close monitoring of patients for symptoms of hypersensitivity or IRRs during and after administration of GDX012 according to study protocol. • Administration of supportive therapy, such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids, per study protocol. • Continued monitoring of patients until complete resolution of signs and symptoms.

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Table 8.a Toxicity Assessment and Management Guidelines

Toxicity	Monitoring, Assessment, and Management Guidelines
HBV reactivation	• Hepatitis virus testing at screening and throughout the conduct of the study as clinically indicated. HBV testing will include HBsAg, HBsAb, and HBcAb. For patients who are HBsAg negative but HBsAb and/or HBcAb positive, HBV DNA will also be assessed at screening. • American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy (and/or local guidelines) • For patients with evidence of viral replication [ie, HBsAg (+), HBV DNA increases, or reverse conversion HBsAg (-) to (+)], consult a specialist to assess the higher risk of hepatic damage and fulminant hepatitis. Antiviral treatment is recommended per clinical guidelines. Hepatic safety monitoring and follow-up for at least 12 months is also recommended. • Antiviral prophylaxis per institutional guidelines is recommended for patients with history of HBV infection.
Lymphodepletion-associated toxicities	Management of lymphodepletion-associated toxicities according to product labeling.

ASTCT: American Society for Transplantation and Cellular Therapy; CARTOX: CAR-T-cell therapy–associated TOXicity; CRS: cytokine release syndrome; GvHD: graft-versus-host disease; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; ICANS: immune effector cell-associated neurotoxicity syndrome; IRR: infusion-related reaction; TLS: tumor lysis syndrome.

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As an additional risk mitigation measure, patients will be required to carry a patient emergency alert card detailing treatment site and investigator contact information, clinical study information, and a back-up 24-hour emergency number. This card is intended to provide relevant contact information should a patient be treated by a nonstudy healthcare provider or emergency-medical services. It will also alert nonstudy healthcare providers to evaluate patients for the potential risks related to the investigational product administration and provide them with the contact information of the treating site and/or obtain important study information relevant to the patient's care. This card will also remind patients of concerning signs or symptoms for which they should seek immediate medical attention. The card will be institutional review board (IRB)-approved before use.

8.6 Definitions of DLTs

DLTs are defined as events meeting the criteria below that occur by Day 30 after the first administration of GDX012 infusion (Day 1). All toxicities will be considered related to GDX012 if they cannot be definitively explained by underlying disease, prior therapy, intercurrent illness or the lymphodepleting chemotherapy regimen.

- Non-hematologic treatment-emergent adverse events (TEAEs):
  - Any Grade 4 non-hematological toxicity.
  - Any Grade 3 non-hematological toxicity involving vital organs (heart, lung, central nervous system).
  - Any Grade 3 non-hematological toxicity that does not resolve to Grade ≤2 within 7 days and is not attributable to underlying illness.
- Grade ≥3 acute or chronic graft vs host disease not completely resolved after 7 days of steroid therapy.
- Grade 4 cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) of any duration as rated per the ASTCT consensus grading.
- Grade 3 CRS or ICANS (as per the ASTCT consensus grading) lasting >72 hours without resolution to Grade ≤2 despite optimal treatment.
- Infusion reaction Grade ≥3 that does not resolve to Grade ≤2 within 72 hours despite optimal treatment.
- Tumor lysis syndrome (TLS) Grade ≥3 except Grade 3 TLS lasting ≤14 days and Grade 4 TLS lasting ≤7 days.
- Persistent cytopenia Grade ≥3 or worsening from Grade 3 at baseline (at screening visit) lasting ≥21 days which is not attributable to underlying disease, intercurrent illness, or prior therapy and does not resolve by Day 45.
- Bone marrow hypocellularity (≤5%) at Day 30 disease evaluation which is not attributable to underlying disease, intercurrent illness, or prior therapy and does not resolve by Day 45.
- Any Grade 5 toxicity attributable to investigational therapy.

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8.7 Safety Monitoring During Phase 2a

During phase 2a of the study, AEs will be monitored starting from the first 5 patients and then every 5 patients up to the approximate maximum number of patients.

AEs that will be monitored during this period include:

- Any Grade ≥3 non-hematologic AE to vital organs (excluding CRS and ICANS) which fails to resolve to Grade ≤2 within 7 days; and is not attributable to the underlying disease.
- Grade ≥3 acute or chronic graft vs host disease not completely resolved after 7 days of steroid therapy.
- Grade 4 CRS or ICANS of any duration as rated per the ASTCT consensus grading.
- Grade 3 CRS or ICANS (as per the ASTCT consensus grading) lasting >72 hours without resolution to Grade ≤2 despite optimal treatment.

- Infusion reaction Grade ≥3 that does not resolve to Grade ≤2 within 72 hours despite optimal treatment.
- Tumor lysis syndrome Grade ≥3 except Grade 3 TLS lasting ≤14 days and Grade 4 TLS lasting ≤7 days.
- Persistent cytopenia Grade ≥3 or worsening from Grade 3 at baseline (at screening visit) lasting ≥21 days which is not attributable to underlying disease, intercurrent illness, or prior therapy and does not resolve by Day 45.
- Bone marrow hypocellularity (<5%) at Day 30 disease evaluation which is not attributable to underlying disease, intercurrent illness, or prior therapy and does not resolve by Day 45.

Accrual to the study will be suspended if:

The above AEs meet the stopping bounds of the number of ≥2/5, ≥4/10, ≥6/15, ≥7/20, 9/25; or

At any time if ≥1 patients present with fatal AEs at least possibly related to GDX012.

After review and consideration by sponsors and investigators, a decision will be made as to whether accrual can be resumed. The stopping bounds for the above AEs are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rules are met, there is at least 70% probability that the true toxicity rate is greater than 30% with a prior beta distribution with parameters 1 and 1 for the binomially distributed toxicity rate.

The pause in enrollment may also necessitate a pause in dosing or termination of the study, depending on the nature and severity of the safety risk. A final decision to resume enrollment and/or amend the protocol will be made by the safety management team after a full review of the safety data. During phase 2a, the safety management team may request review by the independent Data Monitoring Committee (IDMC) as needed.

The study may be halted if the IDMC or any regulatory body decides for any reason that patient safety may be compromised by continuing the study. The study or specific cohort may also be stopped if the futility analysis is met or the sponsor decides to discontinue the development of GDX012.

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8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of GDX012

GDX012 suspension for IV infusion (referred to as GDX012) is a novel allogeneic cell therapy that is enriched for Vδ1^{+} γδ T-cells. [redacted]

It should be noted that leukapheresis donors are screened for communicable diseases in accordance with FDA 21 Code of Federal Regulations (CFR) part 1271. Donors are additionally

tested for cytomegalovirus (CMV; total antibody) and a positive or reactive test is not exclusionary. Results of donor CMV antibody testing will be specified in the documentation that accompanies GDX012 product shipment to ensure that the investigator is aware to inform the patient before use. The investigator should follow any required institutional procedures for subsequent CMV management. Information will also be included in the patient informed consent.

A qualified manufacturing facility will manufacture, package, and label the investigational product in accordance with Good Manufacturing Practice (GMP) and all applicable regulatory requirements.

8.10 [redacted]

[redacted]

8.11 Packaging and Labeling

Product packaging should include the product label, which includes dose information, product release information, and any other necessary product information.

Refer to the cell handling manual for details.

8.12 Storage, Handling, and Accountability

The final product should be stored in a vessel with controlled temperature at or below -130°C and stored in the vapor phase of liquid nitrogen or other sponsor-approved equipment. Refer to the cell handling manual for details.

8.13 Other Protocol-Specified Materials

8.13.1 [redacted]

[redacted]

[redacted]

8.13.2 [redacted]

[redacted]

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, and other vendors such as the interactive response technology provider, may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

For 24-hour contact information, refer to the study manual or equivalent.

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9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC).

9.3 Treatment Group Assignments

In phase 1, up to 18 eligible patients will be sequentially assigned to receive a single IV administration of GDX012 at 1 of 3 planned GDX012 dose levels as identified in Table 4.b.

In phase 2a, eligible patients will be assigned to receive an IV administration of GDX012. If 2 doses are selected from phase 1, initially 20 patients will be randomized in 1:1 fashion across the selected 2 dose levels. After this interim analysis, at most only 1 dose level will be selected to continue the enrollment of 15 additional patients. A maximum of 25 patients for 1 dose level and 35 patients for 2 dose levels will be enrolled following BOP2 design.

For both Phases of the study, patients who achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on ELN 2022 response criteria for AML from the initial GDX012 infusion at Day 30, do not

experience a DLT, and are healthy enough to undergo a second lymphodepletion may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion.

9.4 Study Procedures

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Refer to the Schedule of Events (SOE; Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Screening Phase (Day -21 to Day -6)

Informed consent for participation in the screening phase must be obtained before completion of any study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed before obtaining consent and used to confirm eligibility.

After written informed consent has been obtained, patients will be screened to confirm study eligibility and participation. Only patients who meet the eligibility criteria listed in Section 7.1 and Section 7.2 will proceed to further study procedures.

The screening phase begins on the date the patient (or legally acceptable representative) signs the IRB/IEC-approved ICF and continues through confirmation of eligibility. The screening visit must occur within 21 days before lymphodepleting chemotherapy.

Screening tests will include:

Evaluation of eligibility criteria, disease assessment, and collection of blood and bone marrow:

- Routine assessment: height and weight, vital signs, physical examination, medical history including concomitant medications, complete blood count (differential), blood chemistries, serum immunoglobulins, and coagulation test, serum beta-human chorionic gonadotropin (for women).
- ECOG performance status (Appendix G).

9.4.2 Conditioning Phase (Day -5 to Day -1)

The conditioning phase is defined as the period from lymphodepleting chemotherapy administration to the day before GDX012 administration. Informed consent for study participation with study drug administration must be obtained before lymphodepleting chemotherapy is initiated. Patients must meet all inclusion and exclusion criteria before the treatment with lymphodepleting chemotherapy.

Delivery date of GDX012 to the study site will be confirmed by the sponsor before start of lymphodepleting chemotherapy. For details, see the cell handling manual.

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Patients with symptomatic SARS-CoV-2 infection must not initiate lymphodepleting chemotherapy until recovery from symptomatic infection.

During the conditioning phase:

- Vital signs are evaluated on Days -5, -4, and -3 during the conditioning phase.
- Anti-infective prophylaxis is provided per institutional practices. Antiviral (aciclovir for all patients, lamivudine for patients with prior history of HBV) and antifungal (fluconazole) prophylaxes are recommended or per institutional guidance given expected duration of immunosuppression after administration of lymphodepleting chemotherapy and should be continued for a minimum of 3 months after GDX012 administration. *Pneumocystis jiroveci* pneumonia (cotrimoxazole) prophylaxis is recommended or per institutional guidance for 6 months after GDX012 administration.
- Lymphodepleting chemotherapy before the first dose of GDX012 includes:
  - [redacted] 30 mg/m^2 BSA per day administered IV on Days -5, -4, and -3.

    NOTE: Patients with estimated glomerular filtration rate (GFR) between 30 and 70 mL/min should have a 20% dose reduction of each daily dose of [redacted]. The Modification of Diet in Renal Disease (MDRD) formula should be used to calculate GFR.
  - [redacted] 500 mg/m^2 BSA per day will be administered IV on Days -5, -4, and -3.
- For patients who are to receive a second dose of GDX012, a de-intensified lymphodepleting chemotherapy will be used as follows:
  - [redacted] 25 mg/m^2 BSA per day administered IV on Days -5, -4, and -3.

    NOTE: Patients with estimated GFR between 30 and 70 mL/min should have a 20% dose reduction of each daily dose of [redacted]. The MDRD formula should be used to calculate GFR.
  - [redacted] 300 mg/m^2 BSA per day will be administered IV on Days -5, -4, and -3.

Supportive care before, during, and immediately after administration of lymphodepleting chemotherapy is provided per institutional practices. In case of any relevant delay in the administration of lymphodepleting chemotherapy, continued treatment administration must be discussed with the sponsor's medical monitor. There must be at least 2 chemotherapy-free days between the last day of lymphodepleting chemotherapy and GDX012 administration.

Procedures and assessments to be conducted during the conditioning phase are shown in the SOE (Appendix A). Patients should not experience significant change in clinical status compared with initial eligibility criteria that would, in the opinion of the investigator, increase the risk of AEs associated with experimental cell infusion.

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9.4.3 Treatment and Follow-up Phases (Day 1 to Month 12)

The treatment and follow-up phases begin with GDX012 administration on Day 1 and continue up to Month 12 after the last dose.

- Primary analysis period: 100 days after GDX012 administration of the last patient enrolled in the study.
- Secondary follow-up analysis period (up to 12 months after last GDX012 infusion).

Patients must meet all inclusion and exclusion criteria before treatment with GDX012. Refer to Section 8.10 and Section 8.1 for a description of GDX012 preparation and administration procedures.

Day 1: On Day 1, GDX012 will be administered IV. Premedication may include acetaminophen and an H1-antihistamine according to institutional standards for dimethylsulfoxide-containing cell therapy products. Premedication may be based on the patients risk of hypersensitivity reactions and IRRs. The use of systemic steroids is contraindicated unless required for physiologic replacement. In case of unexpected clinical or logistic reasons, for example, patients experiencing toxicities from the preceding lymphodepleting chemotherapy or delays in GDX012 delivery, GDX012 administration may be delayed for up to 7 days (Section 8.1). In case of delayed GDX012 administration, Day 1 will be defined as the day of actual GDX012 administration.

Vital signs (temperature, heart rate, blood pressure, and respiratory rate) will be obtained for all patients per institutional standard of care for cellular therapy. At a minimum, these measurements should be obtained before GDX012 administration and until the patient is clinically stable, with minimum assessment time points as follows:

- 15, 30, 45, and 60 minutes (±5 minutes) after start of GDX012 administration.
- 1.5, 2, and 3 hours (±10 minutes) after start of GDX012 administration.

Day 1 to Month 12: Following GDX012 administration, all patients will be followed to at least Month 12 in this study. Post treatment evaluations will be conducted during the treatment and follow-up phases as shown in the SOE (Appendix A).

Evaluations may be withheld if the investigator feels that there is a strong contraindication to perform these (eg, the patient has relapsed and is terminally ill). Additional tests and procedures may be performed as clinically indicated.

A patient may complete study participation at any time (Section 9.6). With completion of study participation, the patient will proceed directly to the EOS visit (Appendix A).

Day 30 to Day 45: Primary disease response will be assessed on Day 30 (± 2 days) this will include bone marrow biopsy and aspirate for immunohistochemistry, flow cytometry, morphology, cytogenetics/FISH and molecular studies as well as blood samples for CK and biomarkers as described in the SOE. If the patient has not recovered blood counts on Day 30 and cause cannot be attributed to presence of morphologic disease, a repeat bone marrow aspirate and biopsy will be performed at Day 45 to assess for presence of hyocellularity and cause of prolonged

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myelosuppression. Causes of myelosuppression that may be investigated include, but are not limited to, morphologic AML not seen at Day 30, intercurrent viral infection, and autoimmunity.

Transfusion Support

Following initiation of the lymphodepleting chemotherapy, all blood products for transfusion, with the exception of GDX012, must be irradiated to 3000 cGy to inactivate lymphocytes capable of initiating transfusion-associated GvHD. Blood products are irradiated per institutional guidelines.

9.4.4 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded, as local laws permit, during the screening phase.

9.4.5 Medical History

During the screening phase, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it and the best response achieved by each one. In addition, concomitant medications will be recorded as specified in Section 9.4.10.

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9.4.6 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A). At screening and on Day 1 before GDX012 infusion a complete physical examination, including assessments of the cardiovascular, respiratory, gastrointestinal, neurological, skin, and musculoskeletal systems, will be completed at other time points targeted physical exams can be performed. Any clinically relevant findings will be documented.

9.4.7 Height and Weight

Height will be measured only during the screening phase. Body weight will be measured at the times specified in the SOE (Appendix A).

9.4.8 Vital Signs

Vital sign measurements, including supine (after 3 to 5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and body temperature will be assessed as specified in the SOE (Appendix A). Percutaneous oxygen saturation will also be measured according to the SOE (Appendix A).

9.4.9 Pregnancy Test

A serum pregnancy test will be performed for all women of childbearing potential at screening. Urine pregnancy tests are allowed for subsequent visits. The results must be available and negative before lymphodepleting chemotherapy and treatment with GDX012. For women of childbearing

potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

9.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from the time of informed consent through the end of study (EOS) visit. Refer to Section 8.2 and Section 8.3 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.11 Adverse Events

Monitoring of adverse events (AEs), serious and non-serious, will be conducted throughout the study as specified in the SOE (Appendix A) and in Section 10.3. For patients who receive lymphodepleting chemotherapy and do not receive GDX012, all AEs (regardless of causality) will be collected for the first 30 days; after that, only related AEs will be collected.

Refer to Section 10.0 for details regarding definitions, documentation, and reporting requirements of AEs.

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9.4.12 Enrollment

Enrollment is defined as the time when a patient meets the eligibility criteria and is registered in the study.

9.4.13 12-Lead ECGs and ECHO/MUGA Scans

A single 12-lead standard safety electrocardiogram (ECG) will be performed to assess eligibility as specified in the SOE (Appendix A). ECG assessments are to be performed with the patient supine and rested for 3 to 5 minutes. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

The assessment of left ventricular ejection fraction measured by ECHO or MUGA scan will be performed during screening as indicated in SOE (Appendix A).

9.4.14 Clinical Laboratory Evaluations

Blood samples for analysis of the clinical chemistry and hematology parameters shown below and urine samples for analysis of the parameters will be obtained as specified in the SOE (Appendix A).

A PCR test for SARS-CoV-2 will be performed within 10 days of lymphodepleting chemotherapy initiation as indicated in the SOE (Appendix A). Additional SARS-CoV-2 testing must be conducted for any suspicion of SARS-CoV-2 infection or known exposure. In patients with a history of positive test who are asymptomatic but continue to have a positive polymerase chain reaction (PCR) test result, an antigen test can be used to demonstrate negativity. SARS-CoV-2 testing should follow ASTCT-published guidelines for cellular therapy during the COVID-19 pandemic (Bachanova et al. 2020).

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	aPTT
Hemoglobin	Alkaline phosphatase	Prothrombin time
Leukocytes with differential	ALT	international normalized ratio
Absolute lymphocyte count	AST	
Absolute neutrophil count	Bilirubin (total)	
Platelet count	Bilirubin (direct)	
	Blood urea nitrogen/urea	
	Calcium	
	C-reactive protein	
	Creatinine	
	eGFR (MDRD)	
	Ferritin	
	Glucose	
	Lactate dehydrogenase	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Total protein	
	Uric acid	

ALT: alanine transferase; aPTT: activated partial thromboplastin clotting time; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease.

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Hematology and serum chemistry samples should be drawn locally and reported in the eCRF. All results must be evaluated before dosing.

GFR will be estimated using the MDRD equation. As a backup, creatinine clearance can be determined based on 12 hours or 24 hours collection of a urine specimen. If creatinine clearance is measured for inclusion, it cannot be replaced by the calculated one, if it is more favorable.

In addition to standard clinical chemistry and hematology, virus tests will be performed locally for CMV, HIV, HBV, and HCV according to the SOE (Appendix A). For patients with a medical history of HBV/HCV infection, HBV DNA or HCV RNA must be monitored after GDX012 administration as described in the SOE (Appendix A).

9.4.15 Disease Assessment

Disease assessment per the 2022 ELN response criteria for AML (Appendix F). Disease response will be assessed, as described in the SOE (Appendix A), through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood smears.

9.4.16 CK, Immunogenicity, and Biomarker Samples

9.4.16.1 Primary Specimen Collection

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in the SOE (Appendix A) for CK of GDX012, serum cytokine measurements, and biomarker assessments. On days when lymphodepleting chemotherapy is administered, blood samples should be drawn before dosing. On days when GDX012 is administered follow the SOE for samples that need to be drawn before and after investigational product administration.

Collection of samples for exploratory endpoints are dependent upon local guidelines and regulations (including feasibility of sample export), as well as IRB/EC approval and may not be required on discussion with medical monitor.

Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

9.4.16.2 Bone Marrow Biopsies and Aspirates

Bone marrow aspirates and biopsies, according to the treating institution's guidelines, will be obtained at prespecified time points, as outlined in the SOE (Appendix A).

Screening bone marrow aspirate/biopsy (archived): A bone marrow aspirate and biopsy are required at screening to assess immunohistochemistry, flow cytometry, morphology, cytogenetics/fluorescence in situ hybridization (FISH) and molecular studies. Archived bone marrow biopsy sample (and assessment) within 45 days before the start of lymphodepleting chemotherapy is acceptable if no antitumor therapy was given after bone marrow evaluation. If bone marrow is inasperable, then only a biopsy is required; however, peripheral blood samples should be sent for flow cytometry, cytogenetics/FISH, and molecular studies if blasts are present. Bone marrow biopsy assessment will be performed locally. Exploratory biomarker analyses including, but not limited to, flow cytometry for $V\delta1^+$ $\delta\gamma$ T-cells and other immune cells, RNA for bone marrow profiling, and DNA for MRD will be performed to assess expansion and persistence of $V\delta1^+$ $\delta\gamma$ T-cells, mechanism of action and resistance. Bone marrow biopsy sections leftover from clinical assessments may be requested for further exploratory biomarker assessments.

Posttreatment bone marrow aspirate/biopsy or other tissue samples (fresh): Bone marrow biopsy to assess biomarkers is highly recommended at Day 8 unless the principal investigator or designee assess that it would be unsafe for the patient to undergo this procedure. Primary disease response will be assessed on Day 30 (±2) this will include bone marrow biopsy and aspirate for immunohistochemistry, flow cytometry, morphology, cytogenetics/FISH and molecular studies as well as blood samples for CK and biomarkers as described in the SOE. If the patient has not recovered blood counts on Day 30, a repeat bone marrow aspirate and biopsy should be performed at Day 45 to evaluate for persistent hypocellularity and cause of myelosuppression. Biomarker and CK assessments will be evaluated at this time as per the SOE. Additional, bone marrow assessment is required at Day 100 for assessment of biomarkers and CK. In the event that relapses is suspected, bone marrow aspirate and biopsy should be performed as per the SOE (Appendix A). After Day 100, any bone marrow evaluation done for disease assessment per institutional standard

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of care should be reported in the eCRF. Bone marrow biopsy sections leftover from clinical assessments may be requested for further exploratory biomarker assessments.

9.4.16.3 Tissues Analysis to Evaluate Adverse Events

In the event that tissue samples including but not limited to bone marrow aspirate, lymph node or tumor biopsy, CSF or autopsy tissue are collected clinically for the evaluation of an adverse event samples, if available, may be requested for biomarker assessments.

If second primary malignancy is suspected, a fresh tumor biopsy may be collected for potential donor derived cells.

9.4.17 CK and Pharmacodynamic Measurements

9.4.17.1 Blood Sample for CK

GDX012 cannot specifically be identified in the blood or bone marrow. Hence, CK will be assessed using 1 or more methods including, but not limited to, the following:

- Flow cytometry for $V\delta1^+$ δγ T-cells.
- ddPCR assay to quantify variable delta 1 transcript.
- STR-based chimerism assay to assess for the presence of donor cells.

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For patients treated with GDX012, the CK profile and parameters, including but not limited to C_{max}, t_{max}, t_{last}, and area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}), will be reported, where feasible. The assessment of GDX012 CK will be used to examine the exposure-response relationship, as well as the possible correlation of persistence and expansion of GDX012 with safety and efficacy endpoints. Peripheral blood for CK will be collected as indicated in Appendix A.

9.4.17.2 Homing/Persistence in Bone Marrow

Bone marrow samples for assessment of the presence of GDX012 will be obtained at all time points where bone marrow biopsy/aspirate is prescribed in the SOE (Appendix A). Details of the sample collection procedures for these assays are provided in the laboratory manual. In addition, the presence of $V\delta1^+$ δγ T-cells may be assessed in leftover bone marrow biopsies using techniques including but not limited to ISH/FISH, immunohistochemistry or immunofluorescence.

9.4.17.3 Serum Samples for Cytokines

Serum samples will be collected to monitor the changes in cytokines. Additional soluble factor analyses may be conducted with emerging data. Sample collections for serum cytokines, and inflammatory and safety biomarkers are mandated during the first 28 days following GDX012 administration. Additional unscheduled samples may be collected as needed for further safety

reasons, if it is clinically feasible. Any unscheduled inflammatory markers or laboratory results will be recorded.

9.4.17.4 Blood Samples for TBNK Absolute Counts

Blood samples will be collected for absolute quantification of lymphocytes (T-cells, B-cells, and NK cells) over the course of the study.

9.4.18 Biomarker Measurements

In this study, several biomarker measurements will be assessed to test for correlations with safety and efficacy. These biomarkers will be used for immunogenicity, to establish proof of mechanism and characterize the product post-infusion. The biomarker specimen collection time points are displayed in Appendix A. Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

9.4.18.1 HLA Typing

A blood sample will be collected to extract DNA for HLA typing. In addition, buccal swabs may be requested for germline HLA analysis.

9.4.18.2 Blood Samples for Immunophenotyping

Blood samples will be collected for assessment of GDX012 product post-infusion along with other host immune cells. These blood samples will be analyzed for the presence and changes in immune cell phenotype and/or function, including but not limited to, by flow cytometry and/or molecular techniques including, but not limited to, RNAseq.

9.4.18.3 Immunogenicity Sample Collection

Humoral immunogenicity will be assessed by measuring GDX012 donor-specific, anti-HLA antibodies. Serum samples must be collected before lymphodepleting chemotherapy, and as specified in the SOE (Appendix A) and at unscheduled visits for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/IRR. Antidrug antibody serum sample will be saved for future characterization if applicable. In addition, blood samples may also be collected if IRR/hypersensitivity is observed.

9.4.19 Sample Retention

Bone marrow samples, PBMCs, serum and plasma samples collected as part of the study will be stored and may be used for research purposes up to 15 years after the date of study completion. Samples will be destroyed by a third-party vendor per company standard operating procedures. Samples will be stored according to the laboratory manual. If a patient withdraws consent for study participation and requests that samples collected prior to study withdrawal be destroyed, the investigator needs to inform the sponsor immediately, the samples will be discarded following the local procedure (ie, where the sample resides at the time of withdrawal). The tests performed with these samples are not intended to make determinations about a patient's health or the likelihood

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that a patient will develop any disease, so no test results will be provided to the investigator or put into a patient's medical record. Test results should not be discussed with a patient unless required by local law.

9.4.20 Sample Use for Future Research Purposes

Bone marrow samples, PBMCs, and serum/plasma samples collected as part of the study under sample retention (Section 9.4.19) may be analyzed using new assays or platforms to test hypotheses relevant to disease biology, immuno-oncology, and cell therapy outside of GDX012 clinical study. Research analyses may include, but are not limited to, cell functional assays, targeted DNA and RNA sequencing, immunohistochemistry, and/or flow cytometry.

9.4.21 Healthcare Resource Utilization

Healthcare resource utilization, including hospitalizations and outpatient visits, will be evaluated in this study as an exploratory endpoint. Healthcare resource utilization data regarding hospitalizations and outpatient visits should be collected from all patients, regardless of the reason for the medical care encounter, from the day of screening up to the EOS (ie, Month 12 after final dose of GDX012) for the patient as described in the SOE (Appendix A). Examples of data to be collected include the length of hospital stay (eg, dates of admission and discharge), types of hospital stay (eg, intensive care unit), types of outpatient visits (eg, emergency room visit), and reasons for hospitalization and outpatient visits.

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9.4.22 Patient-Reported Outcomes

In this study, HRQoL impact will be evaluated using the EQ-5D-5L questionnaire.

The EQ-5D-5L questionnaire will be administrated to all patients per the SOE (Appendix A). The preferred method of delivery will be a paper version when patients arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures are performed for that visit. In all instances, patients should complete the questionnaires on their own without any assistance from study site personnel or a caregiver. If there is an extenuating circumstance that requires the patient have the questions read to them, the study site personnel can read the questionnaire and record the responses while patients should respond to the questions on their own.

PRO compliance will be monitored with site trainings conducted, if needed, to ensure data quality. Of note, signs and symptoms assessed with the PRO questionnaire will not be considered AEs unless entered as such into the eCRF.

9.4.22.1 EQ-5D-5L

The EQ-5D-5L (Appendix D) is a self-administered preference-based measure of health status suitable for calculating quality-adjusted life years to inform economic evaluations. EQ-5D-5L includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and 5 response levels for each domain (no problems, slight problems, moderate problems, severe

problems, and extreme problems). Patients are asked to indicate their health state by selecting the most appropriate level of severity on each of the 5 dimensions. Patient responses to the 5 dimensions of the EQ-5D-5L represent the patient's health state that is translated to a utility score using preferably country-specific value sets for the calculation of quality-adjusted life years that are used to inform economic evaluations. There is also a visual analogue scale used by respondents to rate their health on a scale from best (100) to worst (0).

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they receive 2 doses of GDX012 or if they have received 1 dose and have not achieved a response (ie, CR, CRh, CRi, MLFS, or PR) based on 2022 ELN response criteria for AML or have not opted to receive a second permitted dose.

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they had their EOS visit at Month 12 after their last dose of GDX012 or if the patient has been withdrawn from the study (see Section 9.8).

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9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Discontinuation of treatment is applicable during the conditioning phase of the study and during GDX012 administration for a first or second dose. Patients who do not achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on 2022 ELN response criteria for AML and those who opt not to receive a second permitted dose will not be considered to have discontinued treatment.

During phase 1 of the study, patients who discontinue from the study drug or withdraw from the study before the completion of the DLT window for reasons other than experience of a DLT will be replaced in accordance with protocol guidelines in order to achieve the appropriate number of patients in each dose escalation cohort. During phase 2a of the study, patients who withdraw from the study before the Day 30 disease assessment will be replaced in accordance with the guidelines of the study. Patients who withdraw from the study because of progression of disease before Day 30 will be considered non-responders and will not be replaced during phase 2a.

9.8 Withdrawal of Patients From Study

A patient may withdraw from the study at any time at his/her/their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or when it is deemed in their best interest. Withdrawal from the study will have not impact on future medical care at the site.

Withdrawal from the study will be defined as discontinuation from further study visits and procedures at any time after the start of lymphodepletion (regardless of whether the patient receives GDX012).

Best effort should be made to ensure that patients are aware of and willing to comply with all study procedures before initiating screening. Study staff should notify the site monitor and the Sponsor of all trial withdrawls as soon as possible. Reason for withdrawal should be documented in the eCRF.

In the event the patient is lost to follow up, sites should show "due diligence" by documenting in the source documents attempts to contact the patient including dates and methods of contact (eg. Phone calls, e-mails, registered letters).

A patient may be withdrawn from the study for any of the following reasons:

- Death.
- Disease progression requiring alternative therapy.
- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal of consent.
- Non-compliance with the protocol visits or study procedures.
- Other.

All data that has been collected up to that point of study withdrawal will remain in the database and can be subsequently used for analyses. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulation) unless the patient requests samples be destroyed.

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9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of lymphodepleting chemotherapy and study cell product receipt and dispensing.

9.10 Posttreatment Follow-up Assessments (DOR, EFS, OS, and Safety)

All patients who receive GDX012 either in phase 1 or phase 2a of the study will continue to undergo survival assessments. Patients who remain on study should continue visits as outlined in the SOE. Patients who require further treatment not prohibited (see Section 8.2) in the protocol (eg, those who relapse after the primary follow-up period) should remain on study and continue follow-up visits whenever possible. Patients who withdraw from the study for any reason should continue to be assessed for OS unless they have withdrawn consent for future contact.

The OS follow-up should be conducted every 3 months, even outside the scheduled follow-up visits in the SOE. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

The EOS visit is to be completed when the patient discontinues from the follow-up period. See the SOE (Appendix A) for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

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10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to therapeutic intervention or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization (after the initial treatment hospitalization period) or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)

- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective 27 November 2017 (NCI 2017). In addition, grading of CRS and ICANS will follow the ASTCT guidelines (Lee et al. 2019) (Appendix H and Appendix I); grading of acute GvHD will follow the recommendations by the Mount Sinai Acute GvHD International Consortium (Harris et al. 2016); and grading of chronic GvHD will follow the 2014 National Institutes of Health (NIH) Consensus (Jagasia et al. 2015) (Appendix L to Appendix P). For each set of grading criteria, a later version of the criteria may be applied.

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1,000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture

(EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Relationship of the event to study drug administration (ie, the causality assessment) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with (1) the investigational product (GDX012) or (2) conditioning (lymphodepleting) chemotherapy. The relationship is indicated by a yes or no response and entered into the eCRF.

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10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through the EOS visit and recorded in the eCRF.

For patients who receive GDX012, all AEs will be monitored and recorded continuously from signed informed consent through Month 12 after last dose of GDX012/EOS. For patients who receive lymphodepleting chemotherapy and do not receive GDX012, all AEs (regardless of causality) will be collected for the first 30 days following lymphodepleting chemotherapy; after that, only related AEs will be collected.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

A woman must agree not to become pregnant, breastfeed a baby, or donate an egg or eggs (ova) during the study and until at least 12 months following GDX012 administration. If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately. The sponsor must also be contacted immediately by sending

a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to obtain consent from pregnant female partners of patients and to follow the pregnancy through pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, function or stability of a drug product.

An investigator who is made aware of or identifies a potential product complaint should immediately report the event to Takeda in accordance with the contact list provided to the site and recorded in the eCRF. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative. Refer to the appropriate study manual provided separately for additional information (depending on local regulations).

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A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm, whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not.

An overdose is defined as a known deliberate or accidental administration of investigational drug or the lymphodepleting chemotherapy, to or by a study patient, at a dose above that which is assigned to that individual patient according to the study protocol. All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, to capture this important safety information consistently in the database. In the event of drug overdose, the patient should be treated symptomatically.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported per Section 10.2.

The sponsor will also evaluate whether there is a risk that would lead to deaths or SAEs due to the complaint. As a result of the evaluation, the sponsor may ask the investigator(s) for additional investigation. The investigators will need to submit requested follow-up information to the sponsor.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including local health authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the

event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Safety Review Committee

A safety review committee (SRC) will be implemented in phase 1 of this study. SRC meetings will be conducted after each cohort is completed in the dose escalation phase, and approximately once a month in the dose expansion phase, provided patients have been enrolled and data are available to be reviewed. The SRC will review cumulative study safety data and recommend actions regarding dose escalation or dose expansion, study modification for safety reasons, halting and restarting enrollment, study termination, or any other safety-related issues deemed important to study conduct. An SRC charter, defining roles and accountabilities and the process for safety review, will be available.

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11.2 Independent 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 charter before the start of the study.

11.3 Steering Committee

The steering committee will comprise medical experts involved in the study and the sponsor. The steering committee will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality, and making any necessary modifications deemed necessary to the protocol. The steering committee will oversee publications emanating from study results. The steering committee charter will define the responsibilities of the committee.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the

Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

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12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.2 and those documents that include (but are not limited to) the study-specific documents and records such as cell manipulation and storage, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs, including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility.

Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and/or the head of the institution and sponsor.

The sponsor will establish and maintain a system ensuring that the individual product can be traced through the sourcing, manufacture, packaging, storage, transport, and delivery to the hospital, institution, or private practice where the product is used. The sponsor will keep these data for a minimum of 30 years after the expiry date of the product.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

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13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address study objectives.

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

13.2 Determination of Sample Size

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. Approximately 10 to 20 patients may be enrolled in the exploratory cohort(s) to explore alternative conditioning regimen or dose schema.

13.3 Analysis Sets

The analysis sets will include the following:

- ***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.
- ***DLT-evaluable analysis set:*** Patients who were infused with 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 withdraw 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, inform dose level selections for phase 2a and estimate MTD at phase 1.
- ***Response-evaluable analysis set:*** Patients who have received GDX012 administration, have had measurable disease at baseline, and at least 1 posttreatment assessment of disease response or disease progression before the first posttreatment disease assessment. This set will primarily be used for analyses of disease response at phase 2a.
- ***CK analysis set:*** Patients receiving treatment with GDX012 administration and sufficient data to estimate 1 or more CK parameters will be used for CK analyses.
- ***Pharmacodynamic analysis set:*** The pharmacodynamic analysis set will include those patients from the safety analysis set who have baseline and at least 1 postbaseline sample assessment.

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13.4 Analysis of Demographics and Other Baseline Characteristics

Patient disposition, demographic, and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race and other parameters, as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts, and percentages will be provided. Categories for missing data will be presented as needed.

13.5 Efficacy Analysis

Analysis of disease response will be based on the response-evaluable population. Such efficacy endpoints for phase 2a including CR, CRh, CRi, MLFS, and PR will be estimated and presented with a 2-sided 95% exact binomial confidence interval. Estimates of CR, CRh, or CRi will be used to guide interim futility analysis.

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.

13.5.1 Time to Event Endpoints

The analysis of the secondary efficacy endpoints includes DOR, EFS, and OS.

- 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 disease progression or death, whichever comes first. Patients not meeting the criteria for progression or death will be censored at the last disease assessment.
- EFS is defined as the time from the date of the first dose administration to the date of not achieving response, relapse or death from any cause, whichever comes first.
- OS is defined as the time from the date of the first dose administration to the date of death from any cause. Patients who do not die will be censored at the last contact date.

EFS and OS will be analyzed descriptively using Kaplan-Meier method for safety analysis set. DOR will be analyzed using Kaplan-Meier method for patients who experience a CR, CRh, or CRi.

Further details of the analyses of the efficacy endpoints, including sensitivity analyses, censoring rules etc., will be prespecified in the SAP.

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13.6 Safety Analysis

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.

TEAEs are defined as any AE that begins on or after the start date 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.

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 (Lee et al. 2019) (Appendix H and Appendix I), grading of acute GvHD will follow the

recommendations by the Mount Sinai Acute GvHD International Consortium (Harris et al. 2016) and grading of chronic GvHD will follow the 2014 NIH Consensus (Jagasia et al. 2015) (Appendix L to Appendix P). 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 (ie, those events reported by ≥10% of patients).
- SAEs.
- Drug-related SAEs.
- Deaths.
- Drug-related deaths.
- AEs of clinical interest as defined in the SAP.

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

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.

All concomitant medications will be collected and classified to preferred terms according to the WHO Drug Dictionary.

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13.7 CK Analysis

CK-related parameters will be estimated using non-compartmental methods. As permitted by data, CK parameters (eg, C_{max}, T_{max}, AUC_{last}) will be estimated from the measurement of total $V\delta1^+$ γδ T-cells in blood as measured by flow cytometry and/or donor-recipient DNA proportions as measured by an STR-based chimerism assay. CK parameters will be summarized using descriptive statistics. Individual CK concentration-time data and individual CK parameters may be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles may be plotted by dose cohort. The assessment of GDX012 CK will be used to examine the exposure-response relationship, as well as the possible correlation of persistence and expansion of GDX012 with safety and disease response endpoints.

13.8 Immunogenicity Analyses

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

13.9 Exploratory Analyses

13.9.1 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.

13.9.2 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.

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13.9.3 Healthcare Resource Utilization Analyses

Healthcare utilization data will be summarized in descriptive statistics of medical encounters and the number of missing days from work or other activities as reported by patient and caregiver. Further details of the analyses will be provided in the SAP.

13.9.4 PRO Analyses

All PRO analyses will use the safety analysis set. Data per Appendix D will be summarized using descriptive statistics over time. The change from baseline of selected scores will also be summarized using descriptive statistics over time. Compliance will be summarized for each questionnaire by the number of expected and number and percentage of responses received over time and overall.

13.10 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 of CR, CRh, or CRi 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 (ie, 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:

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Table 13.a Optimized Stopping Boundaries

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

The go/no-go criteria in Table 13.a are non-binding. Based on Table 13.a, 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 13.b) of the design using the BOP2 web application (BOP2 V1.4.12.0), which is available at http://www.trialdesign.org.

Table 13.b 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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. If monitors are not allowed to visit sites for data verification due to a pandemic (eg, coronavirus disease 2019 [COVID-19]), remote electronic medical records access visits may be made (where allowed by sites). Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to patients, without prior written agreement with the sponsor or prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the EMA, and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (herein "patients") according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

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15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal-wide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory

documentation and, when applicable, the sponsor has received permission from the competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before

the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

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15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, United Kingdom Medicines and Healthcare products Regulatory Agency, and PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study

information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

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Table 1 Schedule of Events for TAK-012-1501 Protocol

	Screening Phase[a]	Conditioning Phase LDC[b]	GDX012 Administration[b]	First Treatment and Primary Follow-up											Secondary Follow-up[c]		Relapse
	≤21 days Before LDC	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30[c]	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after D30
					±1 d	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3 d	±4 d	±4 d	±7 d	±14 d	
Informed consent	X																
Inclusion/exclusion criteria	X																
Demographics	X																
Medical & Disease history	X																
Physical examination	X	Day -5 (Before LDC)	X	D2 and D4		X		X		X	X			X	X	X	X
Height and weight[d]	X	Day -5 (Before LDC)	X					X		X				X	X	X	X
ECOG performance status	X	Day -5 (Before LDC)						X			X		X	X	X	X	X
Vital signs [e] and SpO_2	X	D -5 to D -3	X[e]	X	X	X	X	X	X	X	X		X	X	X	X	X
12-lead ECG	X	As clinically indicated															
ECHO or MUGA scan	X																
Disease assessment	X										X		X	X	X	X	

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	Screening Phase[a]	Conditioning Phase LDC[b]	GDX012 Administration[b]	First Treatment and Primary Follow-up										Secondary Follow-up[c]		Relapse
	≤21 days Before LDC	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30[c]	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after D30
					±1 d	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3 d	±4 d	±4 d	±7 d	±14 d	
EQ-5D-5L [f]		Day -5 (Before LDC)	X								X		X	X	X	X	X
Concomitant medications and procedures	X																
Adverse Events (AEs)	X																
Healthcare resource utilization	X																
Survival [g]	X																
Laboratory Assessments																	
Hematology, serum chemistry	X	Day -5 and -3 (Before LDC)	X	D2 and D4		X		X		X	X		X	X	X	X	X
Coagulation	X	As clinically indicated															
C-reactive protein, ferritin and cytokines	X	Day -5 (Before LDC)	As clinically indicated														
Virus tests (CMV, HBV, HCV, HIV, HTLV and EBV)	X	As clinically indicated															
SARS-CoV-2 test [h]	X	As clinically indicated															
Creatinine clearance	X																
Pregnancy test [i]	X	Day -5 (Before LDC)	X [j]	As clinically indicated													

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	Screening Phase[a]	Conditioning Phase LDC[b]	GDX012 Administration[b]	First Treatment and Primary Follow-up											Secondary Follow-up[c]		Relapse
	≤21 days Before LDC	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30[c]	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after D30
					±1 d	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3 d	±4 d	±4 d	±7 d	±14 d	
CK and Biomarker Samples																	
Buccal swab – HLA typing	X																
Blood – HLA typing	X																
Blood – CK flow and TBNK		Day -5 (Before LDC)	X[k]	D2 and D4	X	X	X	X		X	X	X	X	X			X
Blood – CK DNA		Day -5 (Before LDC)	X[l]	D2 and D4	X	X	X	X		X	X	X	X	X			X
Serum cytokines		Day -5 (Before LDC)	X[m]	D2 and D4	X	X		X		X	X	X	X	X			X
PBMC – immunophenotyping[n]		Day -5 (Before LDC)	X	D2	X	X		X			X	X	X	X			X
Serum – anti HLA antibodies			X[m]								X	X	X	X			X
BM aspirate – local disease assessment	X[o]										X[o]	X[o, p]		X[o]			X[o]
BM biopsy – local disease assessment	X[o]										X[o]	X[o, p]		X[o]			X[o]
BM aspirate – CK/Immunophenotyping	X					X[q]					X	X[p]		X			X

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	Screening Phase[a]	Conditioning Phase LDC[b]	GDX012 Administration[b]	First Treatment and Primary Follow-up										Secondary Follow-up[c]		Relapse
	≤21 days Before LDC	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30[c]	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after D30
					±1 d	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3 d	±4 d	±4 d	±7 d	±14 d	
BM aspirate – DNA [p]	X					X [q]					X	X [p]		X			X
BM aspirate – RNA	X					X [q]					X	X [p]		X			X
Study Intervention																	
[redacted] 30 mg/m^2		D -5 to D -3															
[redacted] 500 mg/m^2		D -5 to D -3															
GDX012 infusion			X														

AE: adverse event; ALT: alanine aminotransferase; BM: bone marrow; CR: complete response; D: day; EBV: Epstein-Barr virus; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; EQ-5D-5L: European Quality of Life-5-Dimensions-5 Levels; HBV: hepatitis B virus; HCV: hepatitis C virus; HTLV: human T-lymphotropic virus; LDC: lymphodepleting chemotherapy; M: month; MUGA: multigated acquisition scan; PRO: patient-reported outcome; SARS-CoV-2: severe acute respiratory syndrome-coronavirus type 2; SpO2: oxygen saturation; ULN: upper limit of normal.

Tests and procedures should be performed on schedule for all visits. Evaluations and procedures identified in the schedule of procedures may be performed at unscheduled visits, as clinically indicated, at the investigator's discretion in consultation with the sponsor. If a patient is not able to visit the study site, then a telehealth visit should be considered to ensure appropriate oversight and safety monitoring. In addition to this, if the patient is able to visit a local doctor and/or laboratory, then appropriate assessments may be performed at a local laboratory or doctor's office, per investigator discretion.

Day 1 will be defined as the actual day of GDX012 infusion, hence the reference of all subsequent dates.

Footnotes for this table on the next 2 pages.

a Screening must occur within 21 days before the day of LDC. Signed informed consent must be obtained before performing any protocol-specific procedure.

b All assessments must be completed and evaluated before dosing.

c Patients who achieve a response (ie, CR, CRh, CRi, MLFS, or PR) based on 2022 ELN response criteria for AML from the initial GDX012 infusion at Day 30, do not experience a DLT, and are healthy enough to undergo a second lymphodepletion, may receive a second dose of GDX012 may receive a second dose of GDX012 (at the same dose level) at the investigator's discretion. Please follow Table 2. Schedule of Events for Patients Receiving a Second Dose in Appendix A for patients receiving a second dose.

d Height to be measured at screening only.

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	Screening Phase[a]	Conditioning Phase LDC[b]	GDX012 Administration[b]	First Treatment and Primary Follow-up										Secondary Follow-up[c]		Relapse
	≤21 days Before LDC	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30[c]	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after D30
					±1 d	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3 d	±4 d	±4 d	±7 d	±14 d	

e Vital signs should be checked before GDX012 administration and until the patient is clinically stable, at a minimum, 15, 30, 45, 60 minutes (±5 minutes) and 1.5, 2, and 3 hours (±10 minutes) after start of GDX012 administration.

f PROs should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures are performed.

g Survival status will be followed up for all enrolled patients. If a patient misses a scheduled visit, or if the time-point does not align with a scheduled visit, survival status may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

h Polymerase chain reaction SARS-CoV-2 testing within 10 days before LDC. Additional testing must be conducted for any clinical suspicion of SARS-CoV-2 infection or known exposure. To demonstrate a negative test after a positive PCR and resolution of symptoms, an antigen test can be used.

i For women of childbearing potential, a serum pregnancy test will be performed at screening. A urine pregnancy test will be allowed for all other visits. A negative pregnancy test result on Day -5 is necessary before initiation of LDC. If menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

j Pre-dose urine pregnancy test required for women of childbearing potential.

k Blood samples for CK and TBNK to be collected before GDX012 infusion, at 1 hour (±10 minutes), and 3 hours (±10 minutes) after the GDX012 infusion is completed.

l Blood samples for CK DNA to be collected before GDX012 infusion and at 1 hour (±10 minutes), and an optional 3 hours (±10 minutes) after the GDX012 infusion is completed.

m Day 1 cytokine and anti-HLA samples to be collected pre-infusion.

n PBMC for immunophenotyping to be collected only in the dose expansion phase.

o Baseline BM evaluation is required for all patients at screening. Local disease assessment should include morphologic analysis, flow cytometry, cytogenetics/FISH, molecular and surgical pathology If at any time point a bone marrow aspirate cannot be obtained, bone marrow biopsy is sufficient; however, peripheral blood samples should be sent for flow cytometry, cytogenetics/FISH, and molecular studies if blasts are present.

p Bone marrow aspirate/biopsy only required at Day 45 for patients who have not recovered counts at Day 30 to evaluate for persistent hypocellularity and cause of myelosuppression.

q Bone marrow evaluation including aspirate and biopsy are highly recommended at Day 8 unless it would be unsafe for the patient.

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Table 2 Schedule of Events for Patients Receiving a Second Dose

	Conditioning Phase LDC	GDX012 Administration	Second Treatment and Primary Follow-up										Secondary Follow-up		Relapse
	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after Day 30
					±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3d	±4 d	±4 d	±7 d	±14 d	
Physical examination	Day -5 (Before LDC)	X	D2 and D4		X		X		X	X			X	X	X	X
Weight	Day -5 (Before LDC)	X					X		X				X	X	X	X
ECOG performance status	Day -5 (Before LDC)						X			X		X	X	X	X	X
Vital signs and SpO_2	D -5 to D -3	X[a]	X	X	X	X	X	X	X	X		X	X	X	X	X
12-lead ECG	As clinically indicated															
Disease assessment										X		X	X	X	X	X
EQ-5D-5L [b]	Day -5 (Before LDC)	X								X		X	X	X	X	X
Concomitant medications and procedures	X															
Adverse Events (AEs)	X															
Healthcare resource utilization	X															
Survival [c]	X															

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	Conditioning Phase LDC	GDX012 Administration	Second Treatment and Primary Follow-up											Secondary Follow-up		Relapse
	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after Day 30
					±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3d	±4 d	±4 d	±7 d	±14 d	
Laboratory Assessments																
Hematology, and serum chemistry	Day -5 and -3 (Before LDC)	X	D2 and D4		X		X		X	X		X	X	X	X	X
Coagulation	As clinically indicated															
Virus tests (CMV, HBV, HCV, HIV, HTLV and EBV)	As clinically indicated															
SARS-CoV-2 test [d]	As clinically indicated															
C-reactive protein, ferritin and cytokines	Day -5 and -3 (Before LDC)	As clinically indicated														
Pregnancy test [e]	Day -5 (Before LDC)	X [f]	As clinically indicated													
CK and Biomarker Samples																
Blood – CK flow and TBNK	Day -5 (Before LDC)	X [g]	D2 and D4	X	X	X	X		X	X	X	X	X			X
Blood – CK DNA	Day -5 (Before LDC)	X [h]	D2 and D4	X	X	X	X		X	X	X	X	X			X
Serum cytokines	Day -5 (Before LDC)	X [i]	D2 and D4	X	X		X		X	X	X	X	X			X

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	Conditioning Phase LDC	GDX012 Administration	Second Treatment and Primary Follow-up											Secondary Follow-up		Relapse
	D -5, -4, -3	D1	D2 to D4	D5	D8	D11	D14	D17	D21	D30	D45	D60	D100	M6, M9	M12 or EOS Visit	As needed after Day 30
					±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±3d	±4 d	±4 d	±7 d	±14 d	
PBMC – Immunophenotyping[j]	Day -5 (Before LDC)	X[k]	D2	X	X		X			X	X	X	X			X
Serum – anti HLA antibodies	Day -5 (Before LDC)									X	X		X			X
BM aspirate – local disease assessment										X[1]	X[1, m]		X[1]			X[1]
BM biopsy – local disease assessment										X[1]	X[1, m]		X[1]			X[1]
BM aspirate – CK/Immunophenotyping										X	X[m]		X			X
BM aspirate – DNA										X	X[m]		X			X
BM aspirate – RNA										X	X[m]		X			X
Study Intervention																
[redacted] 25 mg/m^2	D -5 to D -3															
[redacted] 300 mg/m (de-intensified LDC)	D -5 to D -3															
GDX012 infusion		X														

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Footnotes for this table on the next page.

AE: adverse event; ALT: alanine aminotransferase; BM: bone marrow; CK: cellular kinetics; CR: complete response; D: day; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: European Quality of Life-5-Dimensions-5 Levels; EOS: end of study; HBV: hepatitis B virus; HCV: hepatitis C virus; HTLV: human T-lymphotropic virus; LDC: lymphodepleting chemotherapy; M: month; MUGA: multigated acquisition scan; PBMC: peripheral blood mononuclear cells; PRO: patient-reported outcome; RNA: ribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome-coronavirus type 2; SpO_2: oxygen saturation; ULN: upper limit of normal.

Tests and procedures should be performed on schedule for all visits. Evaluations and procedures identified in the schedule of procedures may be performed at unscheduled visits, as clinically indicated, at the investigator's discretion in consultation with the sponsor. If a patient is not able to visit the study site, then a telehealth visit should be considered to ensure appropriate oversight and safety monitoring. In addition to this, if the patient is able to visit a local doctor and/or laboratory, then appropriate assessments may be performed at a local laboratory or doctor's office, per investigator discretion.

Day 1 will be defined as the actual day of GDX012 infusion, hence the reference of all subsequent dates.

a Vital signs should be checked before GDX012 administration and until the patient is clinically stable, at a minimum, 15, 30, 45, and 60 minutes (±5 minutes) and 1.5, 2, and 3 hours (±10 minutes) after start of GDX012 administration.

b PROs should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures are performed.

c Survival status will be followed up for all enrolled patients. If a patient misses a scheduled visit, or if the time-point does not align with a scheduled visit, survival status may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

d SARS-CoV-2 testing must be conducted for any suspicion of SARS-CoV-2 infection or known exposure. To demonstrate a negative test after a positive PCR and resolution of symptoms, an antigen test can be used.

e A negative urine pregnancy test result on Day -5 is necessary before initiation of LDC. If menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

f Pre-dose urine pregnancy test required for women of childbearing potential.

g Blood samples for CK by flow and TBNK to be collected before GDX012 infusion, at 1 hour (±10 minutes), and 3 hours (±10 minutes) after the GDX012 infusion is completed.

h Blood samples for CK by DNA analysis to be collected before GDX012 infusion, at 1 hour (±10 minutes), and an optional 3 hours (±10 minutes) after the GDX012 infusion is completed.

i Day 1 cytokine sample to be collected pre-infusion.

j PBMC for immunophenotyping to be collected only in the dose expansion phase.

k Day 1 blood sample for immunophenotyping to be collected pre-infusion.

l Local disease assessment should include morphologic analysis, flow cytometry, cytogenetics/FISH, molecular and surgical pathology If at any time point a bone marrow aspirate cannot be obtained, bone marrow biopsy is sufficient; however, peripheral blood samples should be sent for flow cytometry, cytogenetics/FISH, and molecular studies if blasts are present.

m Bone marrow aspirate/biopsy only required at day 45 for patients who have not recovered counts at Day 30 to evaluate for persistent hypocellularity and cause of myelosuppression.

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Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.

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10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

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Appendix D EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

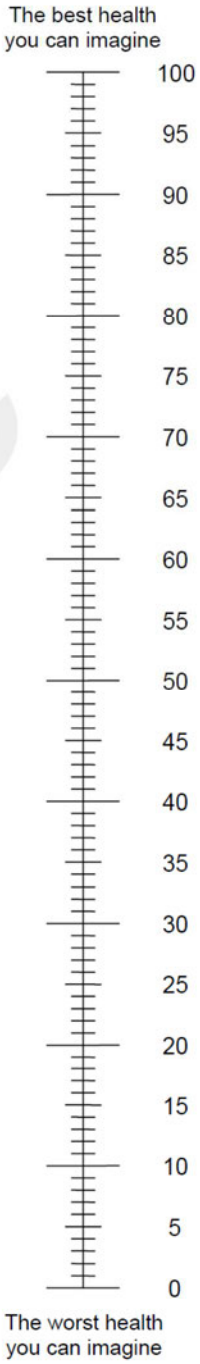
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Sample
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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample
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Source: euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Accessed 22 December 2022.

Appendix E BOIN Design

The Bayesian Optimal Interval (BOIN) design (Liu and Yuan 2015) (Yuan et al. 2016) (Zhou et al. 2018) (Zhou et al. 2020) will be used to guide the dose escalation decisions and MTD estimation. This computation uses shiny app "BOIN" (BOIN V2.7.3.0) available at http://www.trialdesign.org.

The target toxicity rate for the maximum tolerated dose (MTD) is $\phi = 0.3$ and the maximum sample size is 18. Each dose level will enroll at least 3 patients. 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.a), 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.

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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 $j, j = 1,\cdots, J$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the dose escalation for safety. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 6.a, which will be used to conduct the trial.

After the dose escalation is complete, the MTD is selected based on isotonic regression as specified in (Liu and Yuan 2015). Specifically, the dose is selected as the MTD for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, the higher dose level is selected when the isotonic estimate is lower than the target toxicity rate; the lower dose level is selected when the isotonic estimate is greater than or equal to the target toxicity rate.

The operating characteristics of the BOIN design based on 1,000 simulations of each scenario are presented in Table 1.

Table 1. Operating Characteristics of the BOIN Design

	DL1	DL2	DL3	Number of Patients	% Early Stopping
Scenario 1:					
True DLT Rate	0.3	0.48	0.67		
Selection %	70.7	19.7	1.2		8.4
% Patients Treated	64.9	30.4	4.7	9.8	
Scenario 2:					
True DLT Rate	0.13	0.3	0.5		
Selection %	26.2	55.3	18.1		0.4
% Patients Treated	39.6	42	18.3	13.2	
Scenario 3:					
True DLT Rate	0.05	0.13	0.3		
Selection %	3.5	29.3	67.2		0
% Patients Treated	27.4	36.4	36.2	13.6	
Scenario 4:					
True DLT Rate	0.1	0.18	0.25		
Selection %	11.6	27.9	60.2		0.3
% Patients Treated	33.1	35.1	31.8	12.8	

Note: "% Early Stopping" refers to early stopping due to excessive DLT. "Selection %" refers to the percentage of selecting this dose as the MTD. "DL" refers to dose level.

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Appendix F 2022 European LeukemiaNetwork (ELN) Response Criteria in AML

Category	Definition
Complete remission (CR) [a, b, c]	Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1,000/μL); platelet count ≥100 × 10^9/L (100,000/μL)
CR with partial hematologic recover (CRh) [a, b, c]	ANC ≥ 0.5 × 10^9/L (500/μL) and platelet count ≥50 × 10^9/L (50,000/μL), otherwise all other CR criteria met
CR with incomplete hematologic recovery (CRi) [a, b, c]	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1,000/μL]) or thrombocytopenia (<100 × 10^9/L [100,000/μL])
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
No response	Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS, or PR are categorized as having no response prior to the response landmark. Patients failing to achieve response by the designated landmark are designated as having refractory disease
Nonevaluable for response	Nonevaluable for response will include patients lacking an adequate bone marrow response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment
Response if including assessment of MRD)[d]	CR, CRh or CRi with MRD below a defined threshold for a genetic marker by qPCR, or by MFC. Response without MRD should be confirmed with a subsequent assessment at least 4 weeks apart. The date of response without MRD is the first date in which the MRD was below the defined threshold
CR, CRh, or CRi without MRD[c] (CR_{MRD-}, CRh_{MRD-} or CRi_{MRD-})	Response with MRD detection at low-level (CR_{MRD-LL}) is included in this category of CR, CRh, or CRi without MRD. CR_{MRD-LL} is currently only defined for *NPM1*-mutant and CBF-AML

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Category	Definition
Treatment failure	
Refractory disease	No CR, CRh, or CRi at the response landmark, ie, after 2 courses of intensive induction treatment or a defined landmark, eg, 180 days after commencing less-intensive therapy
Relapsed disease (after CR, CRh, or CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least 1 week apart; or development of extramedullary disease

Source: (Dohner et al. 2022).

ANC: absolute neutrophil count; MRD: measurable residual disease; MRD-LL: measurable residual disease-low level.

a. To recognize the potential for continuing improvements in blood counts after myelosuppressive therapy, response definitions for patients with marrow blast clearance (<5%) may be adjusted to reflect the best hematologic response achieved prior to commencement of the next treatment cycle. Aspirate reports that include MLFS, CRh, or CRi should note the potential for post-marrow blood counts to alter the final response designation. Patients should not have received G-CSF, nor platelet transfusions within 7 days prior to hematologic response determination.

b. For patients with CR, CRh, or CRi, the presence of a low percentage of circulating blasts in the blood may represent a regenerating marrow and should not be interpreted as persistent disease. In such cases, the blasts generally disappear within a week.

c. A response landmark for CR, CRh, or CRi should be stated, eg, after 2 cycles of intensive therapy; this landmark may be longer for nonintensive based treatment options, eg, 180 days.

d. MFC-MRD positivity is defined as ≥0.1% of CD45-expressing cells with the target immunophenotype. MRD test positivity by qPCR is defined as cycling threshold (Ct) , 40 and is negative if Ct <40 and is negative if Ct ≥40 in ≥2 of 3 replicates. In *NPM1*-mutated and CBF-AML, CR with molecular MRD detectable at low-level (CR_{MRD-LL}) defined as <2% is designated as negative for MRD, because when measured at the end of consolidation treatment, is associated with a very low relapse rate.

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Appendix G ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: (Oken et al. 1982).

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Appendix H ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [a]	Temperature ≥38°C	Temperature ≥38°C With	Temperature ≥38°C	Temperature ≥38°C
Hypotension	None	Not requiring vasopressors And/or [b]	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow nasal cannula [c] or blow-by	Requiring high-flow nasal cannula [d], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Source: (Lee et al. 2019).

BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events.

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery.

[d] High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

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Appendix I ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score [a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness [b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings [c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Source: (Lee et al. 2019).

CTCAE: Common Terminology Criteria for Adverse Events; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: immune effector cell-associated encephalopathy; ICP: intracranial pressure; NA: not applicable.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
ICE Categories:

- **Orientation:** orientation to year, month, city, hospital: 4 points.
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points.
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point.
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point.
- **Attention:** ability to count backwards from 100 by 10: 1 point.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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Appendix J CARTOX Guidelines for the Management of CRS and ICANS

Management of CRS

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 1	**Fever**	• Assess for infection with blood and urine cultures, and chest radiography • Cardiac telemetry and pulse oximetry	• Acetaminophen and hypothermia blanket as needed for the treatment of fever • Ibuprofen if fever is not controlled with above; use with caution or avoid with thrombocytopenia or renal dysfunction • Empiric broad-spectrum antibiotics and consider filgrastim products if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines • If not on seizure prophylaxis, initiate levetiracetam 500 mg PO twice daily	• Consider tocilizumab[1] for 1 dose for persistent fever lasting greater than 3 days

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CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**

Grade 2	**Hypotension**	• Cardiac telemetry
		• Fever work-up if not previously performed
		  ○ Assess for infection with blood and urine cultures, and chest radiography
			• IV fluid bolus of 500 – 1,000 mL normal saline; repeat once as needed to maintain normal BP
			• If hypotension persists after IV fluids, tocilizumab, and dexamethasone, start vasopressors, transfer patient to IC, obtain ECHO, and refer to further management as in Grade 3 or 4 CSR
			• Symptomatic management of fever as in Grade 1 CRS
			• Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines
				• Administer tocilizumab[1] for 1 dose **and** consider dexamethasone 4 – 10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated
				  ○ Tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period

	Hypoxia	• Pulse oximetry • Fever work-up if not previously performed ○ Assess for infection with blood and urine cultures, and chest radiography	• Use supplemental oxygen as needed • If hypoxia persists after above interventions, but oxygen requirement is stable with low-flow nasal cannula, continue close monitoring. If oxygen requirement increases to high-flow nasal cannula, face mask, or positive pressure ventilation, refer to further management as in Grade 3 or 4 CRS • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Administer tocilizumab[1] for 1 dose **and** consider dexamethasone 4 – 10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated • Tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period

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CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 3	**Hypotension**	• Obtain ECHO if not performed already • Cardiac telemetry • Fever work-up if not previously performed ○ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • IV fluid boluses as needed in Grade 2 CRS • Use vasopressors as needed • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • If on 1 vasopressor: tocilizumab as in Grade 2 CRS and dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) • If vasopressin and norepinephrine equivalent[2] is ≥15 µg/minute, follow as in Grade 4 CRS • Once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Hypoxia	• Pulse oximetry • Fever work-up if not previously performed ○ Assess for infection with blood and urine cultures, and chest radiography	• Supplemental oxygen including high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask as needed • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 CRS if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as per clinical situation • If hypoxia is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below)

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CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 4	**Hypotension**	• Obtain ECHO if not performed already • Cardiac telemetry • Fever work-up if not previously performed ○ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • IV fluid boluses as needed in Grade 2 CRS • Vasopressors as in Grade 3 CRS • Use vasopressors as needed • Symptomatic management of fever as in Grade 1 CRS • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as per clinical situation • If hypotension is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below)
	Hypoxia	• Monitor oxygen saturation while on mechanical ventilation • Fever work-up if not previously performed ○ Assess for infection with blood and urine cultures, and chest radiography	• Transfer patient to ICU • Positive pressure ventilation including CPAP, BiPAP, mechanical ventilation • Symptomatic management of fever as in Grade 1 CRS • Supplemental oxygen including high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask as needed • Symptomatic management of constitutional symptoms and organ toxicities as per standard guidelines	• Tocilizumab[1] as in Grade 2 CRS if not administered previously; tocilizumab may be repeated every 8 hours for up to 3 doses in a 24-hour period • Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as per clinical situation • If hypoxia is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below)

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Management of ICANS

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 1	**Encephalopathy and/or depressed level of consciousness**	• MRI imaging of the brain with and without contrast: CT of brain without contrast may be performed if MRI is not feasible: MRI spine if focal deficits are noted • Neurology consultation • ICE Score assessment every 6 hours or more frequently if clinically indicated • EEG • Consider diagnostic lumbar puncture if other causes of encephalopathy are suspected (eg, infections, autoimmune, leptomeningeal disease) o Add a meningitis-encephalitis panel from CSF in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or if symptoms start after corticosteroids	• Vigilant supportive care; aspiration precautions ; IV hydration • Withhold oral intake of food/medications/fluids and assess swallowing; convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam after EEG is performed (0.25 – 0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used with careful monitoring for agitated patients • If no seizures on EEG, continue prophylactic levetiracetam • If EEG shows focal or generalized convulsive or non-convulsive seizure or convulsive status epilepticus, refer to further management as in Grade 3 or 4 ICANS	• Dexamethasone 10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated o If associated with concurrent CRS, add tocilizumab[1]
Grade 2	**Encephalopathy and/or depressed level of consciousness**	• Neurological work-up as in Grade 1 ICANS	• Supportive care as in Grade 1 ICANS	• Dexamethasone 10 mg IV every 12 hours (or methylprednisolone equivalent) o If associated with concurrent CRS, add tocilizumab[1] • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation

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ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 3	**Encephalopathy and/or depressed level of consciousness**	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging (CT or MRI) every 2-3 days for persistent ≥Grade 3 encephalopathy • Consider diagnostic lumbar puncture if Grade 3 encephalopathy persists ≥2 days or earlier if other causes are suspected (eg, infections, autoimmune, leptomeingeal disease) o Add a meningitis-encephalitis panel from CSR in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or symptoms start after corticosteroids	• Supportive care as in Grade 1 ICANS • Consider ICU transfer • IF there are new abnormal findings on brain imaging[3] not related to primary malignancy, control hypertension with the goal of maintaining mean arterial pressure (MAP) within 20-25 mmHg of baseline MAP, correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/μL, fibrinogen >200 mg/dL and INR <1.5)	• Dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) o If associated with concurrent CRS, add tocilizumab[1] • If Grade 3 encephalopathy is persistent for >24 hours, increase dexamethasone to 20 mg IV every 6 hours (or methylprednisolone equivalent) • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Seizure	• Neurological work-up as in Grade 1 ICANS • EEG if clinically indicated (eg, ongoing seizures, depressed level of consciousness) • Rule out other potential causes of seizure (ie, beta-lactams, etc.)	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive seizures, or non-convulsive seizures, treat as summarized below	• Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) o If associated with concurrent CRS, add tocilizumab[1] • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Focal cerebral edema	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging (CT or MRI) every 24 hours until edema resolves or more frequently if clinically indicated	• Transfer to ICU • Supportive care as in Grade 1 ICANS	• If focal edema is in brain stem or thalamus methylprednisolone 1,000 mg/day in divided doses for IV for 3 days followed by taper depending on clinical situation o If associated with concurrent CRS, add tocilizumab[1] • If focal edema is in other areas of brain, methylprednisolone 1,000 mg/day in divided doses IV for 1 day; assess daily and continue or taper depending on clinical situation • If associated with concurrent CRS, add tocilizumab[1]

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ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
Grade 4	**Encephalopathy and/or depressed level of consciousness**	• Neurological work-up as in Grade 1 ICANS • Repeat neuro-imaging and lumbar puncture as in Grade 3 ICANS	• Transfer to ICU • Supportive care as in Grade 1 ICANS • Consider mechanical ventilation for airway protection • If there are new abnormal findings on brain imaging[1] not related to primary malignancy, control hypertension with the goal of maintaining mean arterial pressure (MAP) within 20-25 mmHg of baseline MAP, correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/µL, fibrinogen >200 mg/dL and INR <1.5)	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • Continue corticosteroids until improvement to less than or equal to Grade 1 ICANS and then taper and stop corticosteroids depending on clinical situation • If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below) including activation of safety switches if applicable
	Seizure	• Neurological work-up as in Grade 1 ICANS • Rule out other potential causes of seizure (ie, beta-lactams, etc.)	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive seizures, or non-convulsive seizures or convulsive status epilepticus, treat as listed below	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below) including activation of safety switches if applicable
	Motor Weakness	• Neurological work-up as in Grade 1 ICANS • MRI with and without contrast of the spine	• Transfer to ICU • Supportive care as in Grade 1 ICANS	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below) including activation of safety switches if applicable
	Diffuse Cerebral Edema or Raised Intracranial Pressure	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging as in focal cerebral edema from Grade 3 ICANS	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For diffuse cerebral edema or signs of raised intracranial pressure, treat as summarized below	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab[2] • If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies (see below) including activation of safety switches if applicable

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Recommendations for Use of IL IL-6 Antagonists and Alternative Agents for Management of CRS and ICANS

Drug	Recommended Dose for CRS and/or ICANS	Maximum Dose	Mechanism of Action	Comments
Tocilizumab	8 mg/kg IV	Maximum 800 mg per dose	IL-6 receptor antagonist	• Maximum of 4 doses total over the entire course of CRS and ICANS • Dose may be repeated every 8 hours for up to 3 doses in a 24-hour period
Siltuximab	11 mg/kg IV once	--	IL-6 antibody	• Recommended primarily for patients who are intolerant to tocilizumab • No more than 1 dose in a 3-week period
Anakinra	100 mg subcutaneously daily for 7 days	--	IL-1 receptor antagonist	• Renal dose adjustment may be needed for creatinine clearance <30 mL/minute
[redacted]	1,500 mg/m^2 IV for 1 dose	--	Alkylating agent	• Give with mesna 1,500 mg/m^2 IV over 24 hours for 1 dose
Anti-thymocyte globulin (rabbit)	1-2 mg/kg IV daily for 3 days	--	Immunosuppressant	• Hypersensitivity reactions can occur; premedicated with diphenhydramine and schedule dose of corticosteroid • No more than 1dose in 3-week period

Management of Focal or Generalized Convulsive or Non Non-Convulsive Seizures

- Assess CAB / consider airway protection / check blood glucose
- Consult Neurology
- For focal and generalized convulsive seizures, lorazepam 1-2 mg IV and repeat as needed (to a maximum cumulative dose of 4 mg)
- For electrographical seizures, including non-convulsive status epilepticus, lorazepam 0.5 mg IV and repeat every 5 minutes as needed (to a maximum cumulative dose of 2 mg)
- Levetiracetam 500-1,500 mg IV bolus (in addition to maintenance dose)
- Replete with magnesium as needed to maintain magnesium level >2 mg/dL
- Thiamine 100 mg IV every 8 hours for 5 days
- If non-convulsive seizures persist, transfer to ICU and add phenobarbital loading dose of 60 mg IV (monitor for respiratory depression, bradycardia and hypotension)
- Maintenance doses after resolution of non-convulsive status epilepticus
  - Lorazepam 0.5 mg IV every 8 hours for 3 doses
  - Levetiracetam 1,000-1,500 mg IV every 12 hours
  - Phenobarbital 30 mg IV every 12 hours (~0.5 mg/kg every 12 hours)
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (ie, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant
    - Target serum trough levels 15-40 µg/mL

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Management of Convulsive Status Epilepticus

- Assess circulation, airway, breathing (CAB) / consider airway protection / check blood glucose
- Transfer to ICU
- Consult Neurology
- Lorazepam 0.1 mg/kg (maximum 4 mg/dose) given at a maximum rate of 2 mg/minute; may repeat in 5 to 10 minutes
- Levetiracetam 500-1,500 mg IV bolus (in addition to maintenance dose)
- Replete with magnesium as needed to maintain magnesium level >2 mg/dL
- Thiamine 100 mg IV every 8 hours for 5 days
- If seizures persist, add phenobarbital loading dose of 15 mg/kg IV (monitor for respiratory depression, bradycardia and hypotension)
- If refractory, consider additional therapies (see below)
- Maintenance doses after resolution of non-convulsive status epilepticus
  - Levetiracetam 1,000-1,500 mg IV every 12 hours
  - Phenobarbital 0.5 mg/kg IV every 12 hours
    - Monitor for respiratory depression, bradycardia and hypotension
    - Assess for drug-drug interactions (ie, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant
    - Target serum trough levels 15-40 µg/mL
- Continuous EEG monitoring if seizures are refractory to treatment

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Management of Diffuse Cerebral Edema and or Raised Intracranial Pressure

For papilledema without diffuse cerebral edema or other signs of raised intracranial pressure	• Acetazolamide 1,000 mg IV followed by 250-1,000 mg IV every 12 hours (monitor renal function and acid/base balance once or twice daily and adjust dose accordingly) • Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) and start taper after resolution of papilledema
For diffuse cerebral edema on neuroimaging or signs of raised intracranial pressure such as decerebrate or decorticate posturing, cranial nerve VI palsy, or Cushing's triad	• Methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated • Elevate head end of patient's bed to an angle of 30 degrees • Hyperventilation to achieve target $PaCO_2$ of 28-30 mmHg, but maintained for no longer than 24 hours • Hyperosmolar therapy with either mannitol (20 g/dL solution) **or** hypertonic saline (3% or 23.4% as detailed below) o Mannitol: initial dose 0.5-1 g/kg IV; maintenance dose 0.25-1 g/kg IV every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours; and withhold mannitol if serum osmolality is ≥320 mOsm/kg or osmolality gap is ≥40) o Hypertonic 3#saline: initial dose 250 mL IV over 15 minutes, maintenance dose of 50-75 mL/hour IV while monitoring electrolytes every 4 hours; withhold infusion if serum sodium levels reach ≥155 mEq/L) o Hypertonic 23.4% saline (for patients with imminent herniation): dose to be administered by physician; initial dose of 30 mL IV; repeat after 15 minutes, if needed • If patient as ommaya reservoir, drain CSF to target OP <20 mmHg • Control hypertension with the goal of maintaining mean arterial pressure (MAP) within 20-25 mmHg of baseline MAP; correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/µL, fibrinogen >200 mg/dL and INR <1.5) • Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on EEG; transfuse to keep platelets ≥100 K/µL if possible and correct coagulopathy in case of surgical intervention • Consider additional therapies (see below) • Metabolic profile every 6 hours and daily CT scans of head without contrast, with adjustments in usage of aforementioned medications to prevent rebound cerebral edema,

	renal failure, electrolyte abnormalities, hypovolemia and hypotension

Source: Adapted from (The University of Texas MD Anderson Cancer Center 2019)

mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf

BiPAP: bilevel positive airway pressure; BP: blood pressure; CAB: circulation, airway, breathing; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; CSF: cerebrospinal fluid; CT: computed tomography; CYP: cytochrome P450; ECHO: echocardiogram; EEG: electroencephalogram; Fio_2: fraction of inspired oxygen; ICANS: immune effector cell–associated neurotoxicity syndrome; ICE: IEC-Associated Encephalopathy; ICU: intensive care unit; IEC: immune effector cell; INR: international normalized ratio; IV: intravenous; MAP: mean arterial pressure; MRI: magnetic resonance imaging; PO: oral; VASST: Vasopressin and Septic Shock Trial.

[1]See Dosing of IL 6 Antagonists and Alternative Agents.

[2]VASST Trial vasopressor equivalent equation : norepinephrine equivalent dose = [norepinephrine (µg/minute)] + [dopamine (µg/kg minute) / 2] + [epinephrine (µg/minute)] + [phenylephrine (µg/minute) / 10]

[3]Abnormal findings on imaging where correction of hypertension hypertension, uremiauremia, andand/or coagulopathy should be performed include changes suggestive of typical or atypical posterior reversible encephalopathy syn drome (PRESPRES), temporal lobe and limbic system encephalitis (autoimmune or infection), acute disseminated encephalomyelitis, embolii, vasculitis, strokes, and/or seizure-related changes.

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Appendix K Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (1):
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation (1):
  - Oral.
  - Injectable.
  - Implantable (2)
- Intrauterine device (2).
- Intrauterine hormone-releasing system (2).
- Bilateral tubal occlusion (2).
- Vasectomized partner (2, 3).
- Sexual abstinence (4).

Methods That are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide (5).
- Cap, diaphragm or sponge with spermicide (5).

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Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

(1) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

(2) Contraception methods that in the context of this guidance are considered to have low user dependency.

(3) Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomized partner has received medical assessment of the surgical success.

(4) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

(5) A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix L Definition of Acute and Chronic GvHD

Category	Time of GvHD Manifestation	Acute GvHD Features [a]	Chronic GvHD Features [a]
Acute GvHD			
Classic acute GvHD	<100 d	Yes	No
Persistent, recurrent, or late-onset acute GvHD	>100 d	Yes	No
Chronic GvHD			
Classic chronic GvHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Source: Adapted from (Filipovich et al. 2005).
GvHD: graft-versus-host disease.
[a] See Appendix M and Appendix O for acute and chronic GvHD features.

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Appendix M Target Organ Staging of Acute GvHD in Adults

Stage	Skin (Active Erythema Only) [a]	Liver (Bilirubin) [b]	Gut (Stool Output/Day) [c]
0	No active (erythematous) GvHD rash	<2 mg/dL	<500 mL/day or <3 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	500-999 mL/day or 3-4 episodes/day or prolonged nausea [d]
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL	1000-1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Source: Adapted from (Harris et al. 2016).

BSA: body surface area; GvHD: graft-versus-host disease.

[a] Use "rule of nines" to determine BSA (head 9%, each arm 9%, front and back torso 18% each, each leg 18%).

[b] Range given as total bilirubin. Downgrade by 1 stage if an additional cause of elevated bilirubin has been

[c] Downgrade by 1 stage if an additional cause of diarrhea has been documented.

[d] With histological signs of GvHD in stomach or duodenum biopsy.

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Appendix N Overall Clinical Grading of Acute GvHD

Grade	Skin	Liver	Gut
0	None	None	None
1	Stage 1-2	None	None
2	Stage 3 and/or	Stage 1 and/or	Stage 1
3	Stage 0-3 and	Stage 2-3 and/or	Stage 2-3
4	Stage 4 and/or	Stage 4 and/or	Stage 4

Source: Adapted from (Harris et al. 2016).

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Appendix O Organ Scoring of Chronic GvHD

Scoring of organ involvement by chronic GvHD will be performed according to the revised NIH criteria of 2014 (Jagasia et al. 2015). Evaluation using a systematic form is recommended:

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

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	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **% FEV1** ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%

Source: (Jagasia et al. 2015).

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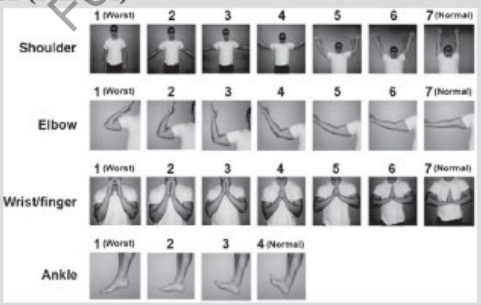
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome	☐ Weight loss>5% * without GI symptoms___	☐ Others (specify):

Overall GVHD Severity *(Opinion of the evaluator)*	❑ **No GVHD**	❑ **Mild**	❑ **Moderate**	❑ **Severe**

Photographic Range of Motion (P-ROM)



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Source: (Jagasia et al. 2015).

Appendix P Global Severity of Chronic GvHD

Overall	Mild	Moderate	Severe
Number of involved organs	1-2	≥3	≥3
Severity of organ manifestation	No more than score 1 and lung score 0	Score 2 or lung score 1	Score 3 or lung score 2-3

Source: Adapted from (Jagasia et al. 2015).

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV_1 (forced expiratory volume in 1 second) is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non–graft-versus-host disease (GvHD) documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

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