Clinical Study Protocol

NCT Number: NCT05020015

Title: A Phase 2, Open-label, Multicenter Study of the Safety and Efficacy of TAK-007 in Adult Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

Study Number: TAK-007-2001

Document Version and Date: Amendment 5, 03 Jun 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 2, Open-label, Multicenter Study of the Safety and Efficacy of TAK-007 in Adult Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

Sponsor: Takeda Development Center Americas, Inc.
500 Kendall Street
Cambridge, MA 02142 USA

Please note: Takeda Development Center Americas, Inc. (TDC Americas) may be referred to in this protocol as "sponsor" or "Takeda".

Study Number: TAK-007-2001

IND Number: 027322

EudraCT Number: 2021-002086-18

Compound: TAK-007

Date: 03 June 2024 **Amendment Number:** 5

Amendment History:

Date	Amendment Number	Amendment Type	Region
03 June 2024	Amendment 5	Substantial	Global
20 December 2023	Amendment 4	Substantial	Global
29 April 2022	Amendment 3	Substantial	Global
21 December 2021	Amendment 2	Substantial	Global
12 July 2021	Amendment 1	Substantial	Global
05 May 2021	Initial protocol	Not applicable	Global

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.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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 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.

[redacted], MD Date
[redacted], Cellular Therapies

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

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

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

[redacted], MD Date
[redacted], Cellular Therapies

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 patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: 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.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 5 Summary of Changes

Protocol Amendment 5 Summary and Rationale

This section describes the changes to the protocol incorporating Amendment 5.

On 11 April 2024, Takeda communicated to the FDA the decision to discontinue the development of TAK-007 in B-cell non-Hodgkin lymphoma. This decision was not due to changes in the safety profile of TAK-007.

The purpose of this amendment is to confirm that:

- All activities to implement TAK-007-2001 Protocol Amendment 4 should be stopped.
- Patient screening will remain closed for new patients, permanently.
- Enrolled patients should continue to be followed per Protocol Amendment 5.
- Secondary follow-up was amended to focus on safety assessments.
- Protocol will implement the long-term follow-up (LTFU) phase for enrolled patients for up to 15 years after TAK-007 administration.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	• Section 6.2 Number of Patients • Section 13.2 Determination of Sample Size	Confirm that the planned number of patients enrolled in study is 45 as of Amendment 5	To clarify that no additional patients will be enrolled in the study.
2	• Section 1.2 Approval	Added Global Safety Lead as signatory.	Added signatory because this is largely a safety-related amendment.
3.	• Section 1.3 Protocol Amendment 5 Summary of Changes	Updated this section with Protocol Amendment 5-specific changes.	To summarize major changes in this amendment.
4.	• Section 2.0 STUDY SUMMARY • Section 6.2 Number of Patients	Revised number of participating sites and countries	To update that the sites will only be US only since Part 2 will no longer be conducted.
5.	• Section 2.0 STUDY SUMMARY	Deleted all references to “Part 1” and “Part 2” of the study, including:	To clarify that Part 2 is no longer part of the study and that

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	• Section 5.1.1 Primary Objective • Section 5.1.2 Secondary Objectives • Section 5.1.3 Exploratory Objectives • Section 5.2.1 Primary Endpoint • Section 5.2.2 Secondary Endpoints • Section 5.2.3 Exploratory Endpoints • Section 6.1 Overview of Study Design • Table 6.b Primary and Secondary Endpoints for Disclosures • Section 8.7 Enrollment Pausing Criteria • Section 9.3 Treatment Group Assignments • Section 9.4.17 Disease Assessment • Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement • Section 9.10 Posttreatment Follow-up Assessments (DOR, PFS, OS, and Safety) • Section 11.1 IDMC • Section 13.2 Determination of	• Revision of post-treatment follow-up assessments. • Revisions in efficacy, safety, and CK analyses. • Deletion of healthcare resource utilization and analyses. • Deletion of patient-reported outcomes (PROs) and analyses. • Deletion of the IDMC Committee. • Deletion of central IRC.	assessments and analyses have been deleted or revised, accordingly.

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Sample Size • Section 13.5 Efficacy Analyses • Section 13.5.1 Efficacy Analysis of the Primary Endpoint • Section 13.5.2 Efficacy Analyses of the Secondary Endpoints • Schedule of Events (Appendix A Table A 1) • Section 13.6 Safety Analysis • Section 13.7 CK Analysis • Section 13.11.1 Population CK-Pharmacodynamic Analysis • Schedule of Events (Appendix A Table A 2)		
6.	• Section 2.0 STUDY SUMMARY • Table 6.b Primary and Secondary Endpoints for Disclosures • Section 6.3.1 Duration of an Individual Patient's Study Participation • Section 6.3.4 Total Study Duration • Section 9.4.3 Treatment and Follow-up Phases (Day 0 to Month 24) • Section 9.4.17 Disease Assessment • Section 9.10	Reduced secondary follow-up phase from 60 months to 24 months, including: • Reducing the number of scheduled visits. • Removing all efficacy-related assessments after Month 6.	To clarify that LTFU phase will begin after Month 24 instead of Month 60, and for up to 13 additional years. To reduce the assessment burden on patients.

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Posttreatment Follow-up Assessments (DOR, PFS, OS, and Safety) • Section 10.3 Monitoring of AEs and Period of Observation • Schedule of Events (Appendix A Table A 1) • Schedule of Events (Appendix A Table A 2)		
7.	• Section 2.0 STUDY SUMMARY	Reduced enrollment period from 4 to 5 years to 3 years.	To clarify that study enrollment is closed and no additional patients are to be enrolled in the study.
8.	• Section 2.0 STUDY SUMMARY • Section 6.1 Overview of Study Design • Section 7.1 Inclusion Criteria, criterion #6 • Section 8.1 Study Drug Administration • Section 8.7 Enrollment Pausing Criteria • Section 9.3 Treatment Group Assignments • Section 13.2 Determination of Sample Size	Revised the number of expansion cohorts	To reflect discontinuation of enrollment to multiple dosing cohorts and non-implementation of Part 2 of the study.
9.	• Section 2.0 STUDY SUMMARY • Section 13.1 General Considerations	Revised primary analysis to not involve any statistical inference.	To clarify how primary analysis will now be assessed.
10.	• Section 8.1 Study Drug Administration • Section 9.4.3	Deleted all references to multiple doses of TAK-007. Deleted the Day 17 scheduled visit	To clarify that patients received only a single dose of TAK-007.

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Treatment and Follow-up Phases (Day 0 to Month 24) • Section 9.5 Completion of Study Treatment (for Individual Patients) • Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement • Schedule of Events (Appendix A Table A 1)	since it is associated with multiple doses of TAK-007.	
11.	• Section 8.4 Precautions and Restrictions • Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Revised pregnancy precautions and restrictions language.	To clarify and ensure consistency current Takeda wording.
12.	• Section 9.4.4.1 RCR Testing • Section 9.4.4.2 TAK-007 Persistence • Section 9.4.19.2 Blood Samples for RCR • Schedule of Events (Appendix A Table A 2) • Schedule of Events (Appendix A Table A 3)	Revised RCR Testing and TAK-007 persistence testing	To clarify reduced testing procedures.

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	• Section 10.3 Monitoring of AEs and Period of Observation • Schedule of Events (Appendix A Table A 3)	Revised AE monitoring and observation period.	To update new monitoring and observation period during the secondary and long-term follow-up.
14.	• Section 2.0 STUDY SUMMARY • Section 6.1 Overview of Study Design • Figure 6.a Study Schematic for TAK-007-2001 Protocol • Section 6.3.1 Duration of an Individual Patient's Study Participation • Section 6.3.4 Total Study Duration • Figure 6.a Study Schematic for TAK-007-2001 Protocol • Table 8.a CAR-T Toxicity Assessment and Management Guidelines • Section 9.4.1 Screening Phase (Day -33 to Day -6) • Section 9.4.3 Treatment and Follow-up Phases (Day 0 to Month 24) • Section 9.4.4 LTFU Phase (Ongoing – up to Year 15 Following TAK-007 Administration) • Section 9.4.18.3 Blood Sample for DNA and Flow Cytometry (CK)	Implement LFTU phase of the study	To clarify that the LTFU phase will begin for all patients who have completed the 2-year secondary follow-up and will continue for up to 15 years after TAK 007 administration to ensure compliance with FDA LTFU guidance for cell therapies studies

Protocol Amendment 5			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	• Section 9.6 Completion of Study (for Individual Patients) • Section 13.1 General Considerations • Schedule of Events (Appendix A Table A 3)		

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-007
Title of Protocol: A Phase 2, Open-label, Multicenter Study of the Safety and Efficacy of TAK-007 in Adult Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma	**IND No.:** 027322 **EudraCT No.:** 2021-002086-18
Study Number: TAK-007-2001	**Phase:** 2

Study Design:

This phase 2, open-label, multicenter study will investigate the safety and efficacy of TAK-007 (anti-CD19 chimeric antigen receptor [CAR]$^+$ natural killer [NK] cellular product) administered intravenously (IV) in adult patients with relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (NHL), including large B-cell lymphoma (LBCL) patients who have failed ≥2 prior systemic therapies (ie, third or higher line [3L+] treatment) and indolent non-Hodgkin lymphoma (iNHL) patients who have failed ≥2 prior systemic therapies (3L+). Eligible patients are required to have previously received an anti-CD20 monoclonal antibody (mAb) and chemotherapy regimen.

At the beginning of the study, the dose escalation phase will be conducted to assess the acute safety profile, cellular kinetics (CK), and pharmacodynamics of the TAK-007 cell product at 2 dose levels (200×10^6 [±30%] and 800×10^6 [±25%] CD19 CAR$^+$ viable NK cells per patient). A sequential dose escalation guided by Bayesian Optimal Interval (BOIN) design will be used, followed by expansion cohorts to select the recommended phase 2 dose (RP2D). Separate expansion cohorts for LBCL and iNHL (Cohorts 1 [LBCL 3L+] and 2 [iNHL 3L+]), with approximately 15 patients each may be initiated for dose level(s) selected based on the dose escalation part, to further evaluate the safety, tolerability, efficacy, and CK and to allow the selection of the RP2D to be used in the rest of the study.

During dose escalation, a 21-day observation period will be placed between the first and the second patient in each dose level, in addition to a 28-day interval between the 2 dose cohorts to allow for dose-limiting toxicity (DLT) assessment.

The sponsor and investigators will select the RP2D. This decision will be based on a review of the preliminary safety and efficacy data generated in the dose escalation and expansion phases.

The study consists of 5 phases: screening, conditioning (lymphodepleting chemotherapy), treatment and primary follow-up (safety and efficacy when patients have had the opportunity to be evaluated for at least 6 months after TAK-007 administration), secondary follow-up (bi-annual safety evaluations for an additional 18 months), and after 2 years, the long-term follow up (LTFU) phase, during which patients will be contacted at least annually for continued monitoring of relevant new safety events. The total duration that an individual patient will participate in this study is 15 years following TAK-007 administration.

Eligible patients will receive lymphodepleting chemotherapy on Days -5, -4, and -3, before receiving a single IV administration of TAK-007 on Day 0.

After TAK-007 administration, response will be assessed locally by computed tomography (CT) and/or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) according to Lugano classification at Months 1, 3, and 6 or per local guidelines until the end of study (EOS).

Clinical evaluations and laboratory studies will be performed on Days 1, 3, and 7 after TAK-007 administration. Clinical evaluation and laboratory studies will be further performed on Days 10, 14, 21, 28, and depending on a patient's response to treatment, Months 2, 3, 4, and 6. After 6 months, during secondary follow up and LTFU, clinical evaluations and laboratory studies will follow an abbreviated Schedule of Events (SOE).

For patients who receive TAK-007, all adverse events (AEs) will be monitored and recorded continuously from signed informed consent through Month 6. After 6 months, during secondary follow-up and LTFU, all related SAEs, deaths, and new incidences of Grade ≥3 AEs that are relevant to the potential risks of TAK-007 will be

collected.

For patients who receive lymphodepleting chemotherapy and do not receive TAK-007, all AEs (regardless of causality) will be collected for the first 30 days following lymphodepleting chemotherapy.

Safety evaluations will include the incidence of AEs, severity and type of AEs, electrocardiograms (ECGs), and changes from baseline in the patient's vital signs and clinical laboratory results at the time points noted in the Schedule of Events (Appendix A).

Grading of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome will be performed following the definition provided in the American Society for Transplantation and Cellular Therapy consensus. Management of immune effector cell therapy-related toxicities will follow the MD Anderson Cancer Center (MDACC) guidelines for the management of CAR-T–cell therapy–associated TOXicity (CARTOX) recommendations.

The overall study schema for TAK-007-2001 is illustrated in Figure 6.a.

Primary Objective:

- To evaluate the safety and tolerability of TAK-007 in adult patients with r/r B-cell NHL to determine the RP2D.

Secondary Objectives:

- To evaluate efficacy endpoints (overall response rate (ORR), complete response [CR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS]).
- To further evaluate the safety and tolerability of TAK-007 in adult patients with r/r LBCL and iNHL.
- To characterize CK of TAK-007.
- To assess pharmacodynamics of TAK-007.
- To assess immunogenicity of TAK-007.

Patient Population: Adult patients with histologically proven B-cell NHL, including LBCL patients who have failed ≥2 prior systemic therapies (ie, 3L+) and iNHL (FL and MZL), including the types defined by the World Health Organization (WHO), who have failed ≥2 prior lines of systemic therapy (3L+).

Number of Patients:	**Number of Sites:**
Approximately 42 patients will be enrolled.	Estimated total: Approximately 15 sites in the United States.

Investigational Therapy:

Dose Escalation: Patients will receive lymphodepleting chemotherapy consisting of IV fludarabine (30 mg/m^2 body surface area [BSA] per day) and cyclophosphamide (300 mg/m^2 BSA per day) on Days -5, -4, and -3 before a single IV administration of TAK-007 (allogeneic cord blood-derived CD19 CAR$^+$ NK cells) at a dose of 200×10^6 (±30%) or 800×10^6 (±25%) CD19 CAR$^+$ viable NK cells on Day 0 of the study.

Dose Expansion Cohort 1 (LBCL 3L+) and Cohort 2 (iNHL 3L+): Patients will receive the lymphodepleting chemotherapy on Days -5, -4, and -3 before the single IV administration of TAK-007 at a dose of 200×10^6 (±30%) or 800×10^6 (±25%) CAR+ viable NK cells on Day 0 of the study.

Period of Evaluation:

Study enrollment: Approximately 3 years.

***Core study (conditioning phase + treatment and primary follow-up phase)*:**
After every patient has had the opportunity to complete at least 6 months of follow-up after TAK-007 administration.

Secondary follow-up phase: After every patient has had the opportunity to complete 24 months of follow-up after TAK-007 administration. Visits will occur at Months 9, 12, 18, and 24.

Long-term follow-up phase: After completion of the 24-month secondary follow-up phase, patients will enter long-term follow-up for up to 13 additional years, for a total duration of up to 15 years after TAK-007 administration.

Main Inclusion Criteria:

1. Patients aged ≥18 years or meeting country definition of adult, whichever is older, at the time of signing the informed consent.
2. Patients who have a life expectancy ≥12 weeks.
3. Patients who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Patients with a diagnosis of previously treated r/r histologically proven CD19-expressing disease of the following types:
   a. ***LBCL,*** including the following subtypes defined by the WHO:
      i. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS).
      ii. High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangement.
      iii. HGBL NOS without translocations.
      iv. DLBCL arising from iNHL including FL or MZL.
      v. T-cell/histiocyte-rich large B-cell lymphoma.
      vi. DLBCL associated with chronic inflammation.
      vii. Epstein-Barr virus–positive DLBCL-NOS.
      viii. Primary cutaneous DLBCL, leg type.
      ix. Primary mediastinal large B-cell lymphoma.
      x. FL Grade 3B.
   b. ***iNHL,*** including the following subtypes defined by the WHO:
      i. FL Grade 1, 2, 3A.
      ii. MZL (nodal, extranodal, and splenic).
5. Patients who have measurable disease, defined as at least 1 lesion per the Lugano classification. Lesions situated in a previously irradiated area are considered measurable if radiographic progression has been documented in such lesions following completion of radiation therapy. LBCL should have a positron-emission tomography–positive disease per the Lugano classification.
6. Patients who have r/r LBCL or r/r iNHL after ≥2 prior lines of systemic therapy (Expansion Cohorts 1 [LBCL 3L+], and 2 [iNHL 3L +]):
   a) Patients with r/r LBCL must have received an anti-CD20 mAb and an anthracycline-containing chemotherapy regimen and failed or be ineligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT).
   b) Patients with iNHL must have received an anti-CD20 mAb and an alkylating agent (eg, bendamustine or cyclophosphamide).
   c) Preinduction salvage chemotherapy and ASCT should be considered 1 line of therapy.
   d) Any consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 line of therapy with the preceding combination therapy. Maintenance antibody therapy should not be considered a line of therapy.
   e) Single-agent anti-CD20 mAb therapy should not be considered a line of therapy.
   f) Bridging chemotherapy given just prior to CAR-T cell therapy treatment should be considered one line of therapy together with cell therapy.
   g) Patients who have received prior CD19-targeting CAR-T cell therapy must have achieved at least a partial response to the most recent CD19-targeting CAR-T cell therapy.
7. Patients who have adequate bone marrow function defined as follows:
   a) Absolute neutrophil count >500/μL.
   b) Platelet count of >50,000/μL at screening. Patients with transfusion-dependent thrombocytopenia are

excluded.

8. Patients who have adequate renal, hepatic, cardiac, and pulmonary function as defined in the study protocol.

Full inclusion criteria are described within the body of the protocol.

Main Criteria for Exclusion:

1. Patients with total body weight of <40 kg.
2. Patients with primary or secondary central nervous system (CNS) involvement by lymphoma. Patients with a history of secondary CNS involvement by lymphoma without evidence of CNS involvement at screening may be included.
3. Burkitt lymphoma, mantle cell lymphoma, lymphoplasmocytic lymphoma, or transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation).
4. Patients with a history of malignancy other than nonmelanoma skin cancer, carcinoma in situ (eg, cervix, bladder, breast), low-grade tumors deemed to be cured and not treated with systemic therapy (eg, by gastro-endoscopy curatively removed gastric cancer) or unless disease free for ≥3 years at screening.
5. Patients who have undergone autologous or allogeneic transplant or CAR-T or CAR-NK cell therapy within 3 months of planned enrollment. Patients after allogeneic transplant have to be off systemic immunosuppressive therapy and without the evidence of clinically relevant acute or chronic graft-versus-host (GvHD) disease at the time of enrollment.
6. Treatment with any investigational products or any systemic anticancer treatment within 14 days or 2 half-lives of the treatment (whichever is longer) before conditioning therapy. For rituximab, a half-life of 22 days should be considered.
7. Patients with active infection**,** including fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management within 3 days before enrollment.
8. Patients with active HIV, hepatitis B virus or hepatitis C virus infection at screening (positive DNA/RNA test).
9. Patients with a history or presence of active or 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.
10. Patients with any of the following within 6 months of enrollment: myocardial infarction, cardiac angioplasty or stenting, unstable angina, symptomatic congestive heart failure (ie, New York Heart Association Class II or greater), clinically significant arrythmia (including uncontrolled atrial fibrillation), or any other clinically significant cardiac disease.
11. Patients with a history of autoimmune disease or solid organ transplantation, requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years.
12. Patients who have received a live vaccine ≤6 weeks before the start of the conditioning regimen.

Full exclusion criteria are described within the body of the protocol.

Main Criteria for Evaluation and Analyses:

The primary analyses of the primary, secondary, and selected exploratory endpoints will be performed at a time when all patients have had the opportunity to be evaluated for at least 6 months after TAK-007 administration. Analyses of the primary, secondary, and exploratory endpoints will also be assessed in the final analysis, if applicable.

Primary Endpoint:

- Incidence of AEs and clinically significant laboratory values and vital signs.

Secondary Endpoints:

- ORR per investigator.
- CR per investigator.

- DOR per investigator.
- PFS per investigator.
- OS.
- CK parameters (eg, maximum observed concentration [C_{max}], time of first occurrence of C_{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), and other parameters as appropriate.
- Pharmacodynamic biomarker assessments utilizing B cell quantification and levels of cytokines in circulation over time.
- Prevalence and incidence of antidrug antibodies (ie, anti–human leukocyte antigens, anti-CAR).
- Prevalence and incidence of replication competent retrovirus positive test results.

Statistical Considerations:

The efficacy analyses will use the modified intent-to-treat (mITT) set to inform the RP2D decision. The analyses of primary and secondary endpoints will be summarized by dose levels in dose escalation cohorts, and by disease cohorts and dose regimens in expansion cohorts.

Sample Size Justification:

The primary analysis for the study does not involve any statistical inference. Consequently, the sample size was determined based on feasibility considerations instead of a formal statistical evaluation.-Approximately 42 patients at levels of either 200×10^6 (±30%) or 800×10^6 (±25%) CD19 CAR^+ viable NK cells per patient will be enrolled.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

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.

3.3 List of Abbreviations

2L	second line treatment
3L+	third or >3rd line treatment
AE	adverse event
ASCT	autologous stem cell transplantation
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
BFI	Brief Fatigue Inventory
BOIN	Bayesian Optimal Interval
BPI	Brief Pain Inventory
BSA	body surface area
BTKi	Bruton tyrosine kinase inhibitor
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T cells
CARTOX	CAR-T–cell therapy–associated TOXicity
CB	cord blood
CFR	Code of Federal Regulation
CK	cellular kinetic(s)
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMSO	dimethylsulfoxide
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

EOS	end of study
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Scale
FACT-GP5	Functional Assessment of Cancer Therapy – General
FDA	[United States] Food and Drug Administration
FDG-PET	^{18}F-fluorodeoxyglucose–positron emission tomography
FL	follicular lymphoma
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GHS/QOL	global health status/quality of life
GI	gastrointestinal
GvHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HGBL	high-grade B-cell lymphoma
HLA	human leukocyte antigen
HRQOL	health-related quality of life
ICANS	immune effector cell-associated neurotoxicity syndrome
iCas9	inducible caspase 9
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL-15	interleukin-15
IND	Investigational New Drug
iNHL	indolent non-Hodgkin lymphoma
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reactions
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
KIR	killer immunoglobulin-like receptor
LBCL	large B-cell lymphoma
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MDACC	MD Anderson Cancer Center
MDRD	Modification of Diet in Renal Disease
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan

MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NK	natural killer (cells)
NOS	not otherwise specified
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3Ki	phosphatidylinositol 3 kinase inhibitor
PMBCL	primary mediastinal large B-cell lymphoma
PP	per-protocol set
PRO	patient reported outcomes
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events
r/r	relapsed or refractory
RP2D	recommended phase 2 dose
RCR	replication competent retrovirus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCT	stem cell transplantation
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{last}	time of last measurable concentration
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Lymphomas account for a heterogeneous group of lymphoid neoplasms with different cellular origins, including B, T, and natural killer (NK) cells. With an incidence of 3% among all cancer entities, lymphomas are considered to be the most prevalent hematological malignancy and responsible for 3% of all cancer-related deaths worldwide (Bray et al. 2018). According to the 2016 revised World Health Organization (WHO) classification of lymphoid neoplasms, lymphomas can be classified into mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, Hodgkin lymphoma, and posttransplant lymphoproliferative disorders, as well as histiocytic and dendritic cell neoplasms (Swerdlow et al. 2016). Within the mature B-cell neoplasms, it can be further distinguished between aggressive (eg, diffuse large B-cell lymphoma [DLBCL] and primary mediastinal large B-cell lymphoma [PMBCL]) and indolent lymphomas (eg, follicular lymphoma [FL] and marginal zone lymphoma [MZL]).

4.1.1 Large B-Cell Lymphoma

DLBCL is the most frequent lymphoma subtype and accounts for approximately one-third of all NHL cases (Sant et al. 2010). It is estimated that approximately 66,000 new cases of NHL and, consequently, approximately 20,000 new cases of DLBCL are diagnosed annually in the United States (US) (Ferlay et al. 2013). Besides the conventional DLBCL not otherwise specified (NOS), several other aggressive large B-cell lymphomas are receiving similar treatment approaches and are together often referred to as large B-cell lymphoma (LBCL). This includes high-grade B-cell lymphoma (HGBL), DLBCL arising from indolent lymphoma including FL or MZL, T-cell/histiocyte-rich LBCL, FL Grade 3B, and PMBCL. As an aggressive lymphoma, LBCL is considered as curable with chemoimmunotherapy (Tilly et al. 2015).

While up to 60% of patients with DLBCL may be cured in the first-line setting with R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone)-based chemoimmunotherapy, the remaining become refractory to treatment or relapse, and the prognosis for these patients is poor (Sehn and Gascoyne 2015). Among patients with progressive disease (PD) during first-line treatment or early relapse after initial response, only 30% to 40% will respond to salvage chemoimmunotherapy and may undergo autologous stem cell transplantation (ASCT) that is necessary for long-term disease control in the relapsed or refractory (r/r) setting (Crump et al. 2014), (Gisselbrecht et al. 2010), (Van Den Neste et al. 2016). The prognosis for patients experiencing failure of second-line salvage therapy is poor, with a median overall survival (OS) of 4.4 months and corresponding 1-year and 2-year OS rates of 23% and 16%, respectively (Van Den Neste et al. 2016).

Even in patients responding to salvage therapy, long-term remissions are only seen in up to 50% (Hamadani et al. 2014), (Gisselbrecht et al. 2012). Furthermore, for patients with refractory DLBCL, the overall response rate (ORR) is 26% and complete response (CR) is 7% to the next line of therapy, with median OS of 6.3 months. Twenty percent of patients are alive at 2 years (Crump et al. 2017). Consolidation of r/r DLBCL patients in remission with allogeneic stem cell transplantation (SCT) may achieve long-term disease control; however, high rates of nonrelapse

mortality and long-term morbidity are expected (Rigacci et al. 2012), (Van Den Neste et al. 2017).

Autologous chimeric antigen receptor T-cell (CAR-T) therapies targeting CD19 have demonstrated efficacy in r/r LBCL after 2 or more prior treatment lines in several phase 2 studies with ORRs and CRs of 72% and 51%, respectively, in the ZUMA-1 study evaluating axicabtagene ciloleucel (Neelapu et al. 2017); 52% and 40%, respectively, in the JULIET study evaluating tisagenlecleucel (Schuster et al. 2019); and 73% and 53%, respectively, in the TRANSCEND NHL 001 study evaluating lisocabtagene maraleucel (Abramson et al. 2020). Two-year follow-up data from the ZUMA-1 study showed a median progression-free survival (PFS) of 5.9 months, and 58% (59 of 101) of patients achieved CR (Locke et al. 2019). Importantly, these outcomes are focusing on patients treated with CAR-T cells and not the complete intent-to-treat (ITT) population with patients who were not treated in the study (eg, due to manufacturing failure, PD, or death while waiting for the cell therapy product). Furthermore, Grade ≥3 cytokine release syndrome (CRS) occurred in 11% of patients, and Grade ≥3 neurological events occurred in 32% of patients. As evidenced by the results of these published studies, the wide application of autologous CAR-T adoptive cell therapy is limited by significant toxicities (including but not limited to CRS and neurotoxicity), reimbursement issues, and significant logistical challenges of autologous cell collection, manufacturing, and infusion.

Allogeneic, off-the-shelf, CAR-T cells might overcome the logistical limitations of autologous CAR-Ts but pose other critical challenges, including risk of graft-versus-host disease (GvHD) and graft rejection; CAR-T cells also require complex gene editing procedures to reduce toxicity. Importantly, the outcome of patients failing CD19-targeted CAR-Ts is poor with a median OS of only 5.3 months (Chow et al. 2019). Recent data indicate the potential benefit of retreatment of CD19 CAR-T therapies in a minority of patients and only with limited response duration in LBCL (Gauthier et al. 2021).

Meanwhile, noncellular therapy in heavily pretreated patients with LBCL has made variable progress. Monotherapies, as well as drug combinations, may achieve decent response rates in this heavily pretreated patient population. Examples include selinexor (ORR 28%) (Kalakonda et al. 2020), loncastuximab tesirine (ORR 48%) (Caimi et al. 2020), polatuzumab vedotin/bendamustine/rituximab (ORR 63%) (Sehn et al. 2020), and tafasitamab/lenalidomide (ORR 60%) (Salles et al. 2020). Nevertheless, new treatment options are still needed for patients to achieve long-term benefit with an improved safety profile.

In summary, there remains a significant medical need for patients with r/r LBCL, and novel treatment approaches are needed to improve outcomes for these patients.

4.1.2 Indolent Non-Hodgkin Lymphoma (FL and MZL)

FL and MZL are considered to be incurable indolent mature B-cell malignancies, affecting approximately 30,000 new patients annually in the US. FL and MZL are heterogeneous diseases with varying prognoses, owing to differences in clinical, laboratory, and disease parameters.

Localized FL is treated with radiation in curative intent (Lowry et al. 2011). Treatment of systemic disease is indicated in the presence of lymphoma-related symptoms (eg, B symptoms,

hematopoietic insufficiency, rapid lymphoma progression, and organ compression). Treatment goals in advanced indolent non-Hodgkin lymphoma (iNHL) are to provide a durable remission and to contribute to improved outcomes by offering longer PFS, with minimum side effects. Current standard of care in the first-line setting for fit patients is chemoimmunotherapy including a CD20 antibody (eg, rituximab, obinutuzumab) and an alkylating agent (eg, bendamustine, cyclophosphamide). Definitive management of r/r iNHL remains controversial due to the large number of available treatment options, such as chemotherapy, radioimmunotherapy, targeted therapies, ASCT, and allogeneic SCT.

Recent data identified that one of the strongest predictors of long-term FL outcomes is length of first remission after first-line therapy. Patients with progression of disease within 24 months of completing induction chemoimmunotherapy (POD24), who make up approximately 20% of patients, have significantly poorer outcomes than those with longer remission durations (5-year OS: 50% versus 90%, respectively) (Casulo et al. 2015). The prognosis for patients with iNHL relapsing or refractory to second-line and third-line of therapy is poor, with 5 year OS dropping to 40% to 45%. Use of phosphatidylinositol 3 kinase inhibitors (PI3Ki) in patients relapsing after 2 or more previous lines of therapy has demonstrated encouraging ORRs (copanlisib, 59%; duvelisib, 42%; idelalisib, 56%); however, with median PFS of 12.5, 9.5, and 11 months, respectively, the duration of response (DOR) is relatively limited (Dreyling et al. 2020), (Flinn et al. 2019), (Gopal et al. 2014). The EZH2 inhibitor tazemetostat displayed only limited activity in EZH2 wild-type FL (ORR 34%) (Morschhauser et al. 2020). For those patients who achieve remission with salvage therapy, ASCT may be considered. For subsequent remissions or one requiring more than 2 lines of therapy, allogeneic SCT may be discussed depending on younger patient age and the absence of comorbidities. FL management in the r/r disease setting is influenced by initial first-line therapy and the duration and quality of the response.

MZL is subdivided into 3 major categories: extranodal MZL of mucosa-associated lymphoid tissue, nodal MZL, and splenic MZL representing 70%, 20%, and 10% of all MZL, respectively (Bertoni et al. 2011). For localized disease, recommended therapies include triple therapy for *Helicobacter pylori* in gastric extranodal MZL, splenectomy for splenic MZL, and radiotherapy for nodal MZL. For disseminated disease with low tumor burden, a watch-and-wait approach or single-agent rituximab may be applied. For symptomatic disease, however, a similar approach to FL is used with chemoimmunotherapy approaches such as bendamustine and rituximab. Patients with relapsing disease after at least 1 CD20-targeted therapy have chemotherapy-free options available, including the Bruton tyrosine kinase inhibitor (BTKi), ibrutinib (ORR 48%) (Noy et al. 2017), the PI3Ki umbralisib (ORR 49%) (Fowler et al. 2021), and the immunomodulatory agent lenalidomide in combination with rituximab (ORR 65%) (Leonard et al. 2019).

Transformation from an indolent to more aggressive disease is also a well-recognized complication of iNHL in the natural disease history. Transformation is defined by histologic evidence of DLBCL or other high-grade morphology, usually accompanied by rapid progression of lymphadenopathy, extranodal disease outside the marrow, B symptoms, and elevated serum lactate dehydrogenase.

Cellular immunotherapy, such as CD19-targeted CAR-T cells, may be a treatment option for r/r iNHL. In the ongoing phase 2 ZUMA-5 study of axicabtagene ciloleucel with 96 evaluable patients (80 patients with FL and 16 patients with MZL), ORR was 93% with 80% CR (Jacobson et al. 2020). The median PFS was 23.5 months for all patients (23.5 months and 11.8 months for patients with FL and MZL, respectively). Furthermore, in the ongoing phase 2 ELARA study of tisagenlecleucel with 98 FL patients, ORR was 83% with 65% CR (Fowler et al. 2020).

Published reports suggest that CAR-Ts may be an option for multiply relapsed patients. However, significant toxicities, including CRS and neurotoxicity, and significant challenges to logistics of autologous cell collection, manufacturing, and infusion have limited wide application of autologous CAR-T therapy.

Taken together, there is still a significant medical need for patients with iNHL. Novel treatment approaches are necessary to improve outcomes in these patients.

4.1.3 TAK-007 and Rationale for Development in Patients With r/r B-cell NHL

TAK-007 is a cryopreserved allogeneic cellular product comprising human umbilical cord blood-derived natural killer (CB-NK) cells genetically modified with retroviral vector SFG.iC9.2A.CAR.CD19-28-3zeta.2A.IL15 encoding the transgenes for anti-CD19 chimeric antigen receptor (CAR), the CD28 endodomain, the ζ-chain of the T-cell receptor (TCR) complex, interleukin-15 (IL-15), and inducible caspase 9 (iCas9)-based safety switch. TAK-007 is designed to be administered in conjunction with lymphodepleting chemotherapy in patients with r/r $CD19^+$ B-lymphoid malignancies (eg, LBCL, FL, MZL). A phase 1/2 study of anti-CD19 CAR^+ NK cells derived from cord blood (CB) in adult patients with r/r $CD19^+$ cancers was conducted using fresh formulation of this cellular product at the MD Anderson Cancer Center (MDACC) (refer to NCT03056339 for details).

NK cells are highly cytotoxic effectors of innate immunity, killing their targets in a nonantigen-specific manner, whereas the adaptive cytotoxic functions of T cells depend on antigen activation. Unlike allogeneic T cells that carry a significant risk of GvHD mediated through the TCR activation, NK cells are characterized by a lack of TCR, hence, have limited potential to cause GvHD. CD19 CAR^+ NK cells can target lymphoma cells via CD19 antigen-specific CAR-driven and innate nonantigen-specific mechanisms and may become a novel therapy. CB offers an attractive source of allogeneic and off-the-shelf NK cells for immunotherapy. Transduced CB-NK cells expressing CD19 CAR and IL-15 have demonstrated killing of CD19-expressing cell lines and primary leukemia cells in vitro, with prolongation of survival in a xenograft Raji lymphoma murine model. IL-15 production by the transduced CB-NK cells increased their persistence and tumor control (Liu et al. 2018).

Treatment goals in r/r NHL are to provide a durable remission by offering longer PFS with minimal side effects. However, currently available treatment options for patients with r/r aggressive and indolent B-cell lymphoma are unsatisfactory resulting in continued major unmet medical need.

4.1.4 Nonclinical Experience

TAK-007 uses the genetically identical CAR construct transduced with the same viral vector used in the MDACC CD19 CAR^+ NK study (Clinical Protocol 2016-0641) but differs in that it uses a semi-closed and scalable manufacturing process and is developed as a cryoformulation. The nonclinical studies conducted in support of TAK-007 include a series of in vitro and in vivo studies to investigate efficacy, pharmacodynamics, cellular kinetics (CK), and safety.

In vitro studies conducted with TAK-007 characterized the CAR expression, the cellular composition, IL-15 secretion, iCas9 functionality and cytolytic activity of TAK-007. These studies confirmed the presence of a high percentage of NK cells, CAR-expression on NK cells, IL-15 secretion, and low levels of non-NK cells in the composition of TAK-007. In addition, TAK-007 demonstrated cytolytic activity against both $CD19^+$ and $CD19^-$ cells. CAR-independent killing of cancer cells was robust and could be augmented by addition of the CAR. CAR-independent killing of primary B cells was minimal, in line with low to undetectable levels of stress ligands expressed by these cells.

In vivo efficacy and tolerability/toxicity studies with TAK-007 were conducted using the aggressive systemic luciferase-expressing Raji human Burkitt's lymphoma xenograft model in whole body irradiated nonobese diabetic severe combined immunodeficient gamma (NSG) mice. Doses in the in vivo studies bracket the clinical doses based on a total cells/kg basis and represent the doses of total NK cells required for nonclinical efficacy in this model. TAK-007 demonstrated anti-tumor activity; maximum whole blood TAK-007 CAR^+ cells concentrations were dose dependent and observed on Day 1 postdose; TAK-007 CAR^+ cells were detected in tissues on Days 14 and 22; and plasma concentrations of human IL-15 were below the quantification limit at all timepoints in all groups. No TAK-007-related toxicity findings were observed.

The risk of genotoxicity is low based on the safety features included in the design of the viral vector, the absence of replication-competent retroviral vector in the drug product, a highly polyclonal viral vector integration profile, and normal karyotype of TAK-007. Furthermore, TAK-007 did not demonstrate IL-2/IL-15 independent proliferation, and low levels of cellular impurities including $CD34^+$ and universal antigen-presenting cells that may carry a risk of second primary malignancy are being controlled during the manufacturing process.

Nonclinical data show that TAK-007 (i) expresses the CD19 CAR on the cell surface, (ii) is functional with regards to IL-15 secretion, killing of $CD19^+$ and $CD19^-$ tumor cells, and iCas9 elimination of CAR^+ cells, (iii) has an impact on $CD19^+$ tumor growth in an immunocompromised mouse model of human Burkitt's lymphoma, (iv) is generally well-tolerated in vivo, and (v) has a low risk of tumorigenicity.

Nonclinical study results and detailed nonclinical study information are provided in the TAK-007 Investigator's Brochure.

4.1.5 Clinical Experience

MDACC conducted a phase 1/2 CD19 CAR$^+$ NK study (Clinical Protocol 2016-0641) entitled, "Dose Escalation Study Phase I/II of Umbilical Cord Blood -Derived CAR-Engineered NK Cells in Conjunction with Lymphodepleting Chemotherapy in Patients with Relapsed/Refractory B-Lymphoid Malignancies." This study used fresh CD19 CAR$^+$ NK product with CB-derived NK cells engineered to express anti-CD19 CAR, IL-15, and iCas9-based safety switch. Postremission therapy was permitted after the Day 30 assessment at the treating physician's discretion. The first 9 patients received a CAR$^+$ NK product that was partially human leukocyte antigen (HLA)-matched with the recipient (4/6 HLA molecules: HLA-A, B, and DRβ1); the protocol was then amended to permit treatment with no consideration for HLA matching (infused Patients 10 and 11). When possible, a CB unit with killer immunoglobulin-like receptor (KIR)-ligand mismatch was selected for CAR$^+$ NK production.

Initial results from this ongoing study were reported by Liu and colleagues (Liu et al. 2020). From June 2017 to February 2019, 11 patients were treated; the median age was 60 years (range, 47 to 70 years). Five patients had chronic lymphocytic leukemia (CLL) (2 had Richter's transformation or accelerated CLL) and all had failed ibrutinib plus a minimum of 3 prior lines of therapy. All 5 patients had high-risk cytogenetic characteristics. Six patients had lymphoma, including 2 with DLBCL and 4 with the FL; 3 of these patients underwent transformation to high-grade lymphoma. Of the 6 patients with lymphoma, 4 had undergone disease progression after autologous hematopoietic stem-cell transplantation and 2 had refractory disease.

None of the patients developed CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), or hemophagocytic lymphohistiocytosis. Moreover, no cases of GvHD were noted despite the HLA mismatch between the patients and their CAR$^+$ NK cell products. As expected, all patients had hematologic toxicity secondary to the lymphodepleting chemotherapy. No cases of tumor lysis syndrome (TLS) or Grade III/IV nonhematological toxicity attributable to the CAR$^+$ NK product were observed. The maximum tolerated CAR$^+$ NK cell dose was not reached. No patient required admission to an intensive care unit for management of CAR$^+$ NK cell toxicity, and there was no need for steroids or anti-IL-6 therapy (tocilizumab), and no need to activate the iCas9 safety switch. Patient 2, however, required intensive care for progressive lymphoma and died of the malignancy.

At a median follow-up of 13.8 months, 8 of the 11 treated patients (73%) had objective responses (4 of 5 CLL and 4 of 6 NHL) with 7 (64%) achieving a CR. Responses were rapid, usually within 30 days of administration, and seen at all 3 dose levels examined. Despite the limitations imposed by a small sample size, these results compare favorably to those reported for anti-CD19 CAR T-cells in the same patient population.

In summary, these early results of a first-in-human phase 1/2 study of CB-derived NK cells engineered to express an anti-CD19 CAR, IL-15 and an iCas9 safety switch is well tolerated with preliminary evidence of activity in heavily pretreated patients with multiply r/r CLL or NHL.

Since this January 2020 publication, MDACC continued to enroll and treat patients on the 2016-0641 study. Patients have continued to show responses, and the ongoing tolerance and

safety experiences have been generally favorable and consistent with the initial report. So far, there has been no need to activate the iCas9 safety switch; 1 instance of Grade 1 CRS lasting approximately 24 hours was reported, and there have been no reported cases of neurotoxicity or GvHD (communication with MDACC).

TAK-007-2001 is the only study to date of the TAK-007 cryopreserved allogeneic CAR-NK cell therapy in humans that uses CB-derived NK cells. The first patient was dosed in August 2022 and the study has enrolled 21 patients with LBCL and iNHL as of 8 July 2023. Nine patients received TAK-007 during the dose escalation phase, including 3 patients who received TAK-007 at the 200 M CAR^+ NK cell dose level, and 6 patients at the 800 M CAR^+ NK cell dose level. A further 12 patients were dosed in the expansion phase at 800 M CAR^+ NK cells.

4.1.6 Known and Potential Benefits and Risks to Patients

This is the first study in which TAK-007 therapy will be given to humans. Nonclinical laboratory testing and clinical studies with fresh CD19 CAR NK cell therapy have not identified any serious risks. The safety profile of fresh CD19 CAR NK cell therapy in humans is still evolving. Safety data from the initial Dose Escalation and Expansion cohorts of this study are available in the Investigator's Brochure.

The following risks are based on those observed in patients receiving CD19 CAR-T therapies. TAK-007 is expected to have a lower toxicity profile compared with CD19 CAR-T therapies, and the following events are expected to be less frequent and less severe, but still may occur in patients receiving TAK-007 therapy:

- CRS, which can be associated with serious events, including cardiac failure, kidney dysfunction, capillary leak syndrome, hypoxia, and very rare events such as hemophagocytic lymphohistiocytosis and macrophage activation syndrome.
- GvHD.
- Neurological syndromes, including ICANS. Associated symptoms may include altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding, loss of balance, and/or encephalopathy.
- TLS.
- Hypersensitivity reactions and infusion-related reactions (IRRs). Symptoms of allergic reaction may include a rash, hives, pyrexia, shortness of breath, and hypotension, which can be confused with CRS. Signs and symptoms of IRRs may also include wheezing, chest pain, pruritis, rigors, and gastrointestinal (GI) symptoms.
- Replication competent retrovirus (RCR) positivity and risk of second primary malignancy.

TAK-007 is administered after lymphodepleting chemotherapy, and therefore TAK-007 therapy includes risks associated with fludarabine and cyclophosphamide. The risks associated with lymphodepleting chemotherapy include the following:

- Viral reactivation, including hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, varicella zoster virus, and cytomegalovirus (CMV) reactivation (potential risk).
- Severe or prolonged cytopenias resulting in anemia (fatigue, shortness of breath), neutropenia (severe infections), and thrombocytopenia (bleeding, hemorrhage).
- GI disturbances (nausea, vomiting, diarrhea).

TAK-007 toxicities are expected to be less severe compared to the currently approved CAR-T therapies and manageable according to standard medical practices and published guidelines, including the MDACC guidelines for the management of CAR-T–cell therapy–associated TOXicity (CARTOX) (The University of Texas MD Anderson Cancer Center 2019). Standard-of-care treatments for cell-therapy toxicities are effective for the management of safety concerns in commercially available CAR-T therapies, which have a high risk of CRS and ICANS compared to CAR-NK cells.

4.2 Rationale for the Proposed Study

As mentioned previously, the use of autologous CAR-T cells is accompanied with significant challenges in logistics for personalized and timely cell product manufacture and administration. Allogeneic CAR-T cells with encouraging results in early-stage development can help to improve the logistic challenge, but the risk of GvHD is still of concern. TAK-007, an allogeneic, off-the-shelf, CD19 CAR$^+$ NK cell product, presents a potential novel NHL therapy via CD19 antigen-specific and innate nonantigen-specific mechanisms with a favorable safety profile compared with CAR-T therapies. MDACC investigators have conducted Investigational New Drug (IND)-enabling nonclinical studies of umbilical CB-NK cells transduced with a viral vector incorporating the genes for CD19 CAR, IL-15, and iCas9-based suicide gene. This group's early phase 1 data demonstrate clinical efficacy in r/r LBCL and iNHL patients without evidence of clinically relevant GvHD, CRS, or neurotoxicity (Liu et al. 2020).

On the basis of these early findings, it is expected that TAK-007 (allogeneic SFG.iCas9.2A.CAR.CD19-28-3zeta.2A.IL15-transduced CB-NK cells with cryopreservation) administered after lymphodepleting chemotherapy in patients with r/r LBCL and iNHL will provide equivalent or higher rates of disease response than expected with current standard of care. Occurrence of CRS and neurotoxicity complications like those associated with current autologous CAR-T therapies are also expected to be significantly lower, representing a meaningful clinical benefit for patients with r/r LBCL and iNHL. Occurrence of GvHD is expected to be significantly lower compared with allogeneic CAR-T. This allogeneic CAR$^+$ NK approach should greatly improve the logistics of delivering this therapy to large numbers of patients, a major limitation of current autologous CAR-T therapies, hence the rationale for the proposed clinical study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the safety and tolerability of TAK-007 in adult patients with r/r B-cell NHL to determine the recommended phase 2 dose (RP2D).

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate efficacy endpoints (ORR, CR, DOR, PFS, and OS).
- To further evaluate the safety and tolerability of TAK-007 in adult patients with r/r LBCL and iNHL.
- To characterize CK of TAK-007.
- To assess pharmacodynamics of TAK-007.
- To assess immunogenicity of TAK-007.

5.1.3 Exploratory Objectives

The exploratory objectives are:

- To conduct population CK/pharmacodynamics modeling to further evaluate the relationship between exposure and response (safety, efficacy, pharmacodynamics, and product attributes).
- To explore biomarkers of clinical response including predictive biomarkers, mechanism of action, mechanism of resistance, and product performance.

5.2 Endpoints

5.2.1 Primary Endpoint

- Incidence of adverse events (AEs) and clinically significant laboratory values and vital signs.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- ORR per investigator.
- CR per investigator.
- DOR per investigator.
- PFS per investigator.

- OS.
- CK parameters (eg, 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 [t_{last}]), area under the concentration-time curve from time 0 to time of the last quantifiable concentration [AUC_{last}]), and other parameters as appropriate.
- Pharmacodynamic biomarker assessments utilizing B cell quantification and levels of cytokines in circulation over time.
- Prevalence and incidence of antidrug antibodies (ie, anti-HLA, anti-CAR).
- Prevalence and incidence of RCR positive test results.

5.2.3 Exploratory Endpoints

The exploratory endpoints are:

- Characterization and evaluation of predictive biomarkers, as well as molecular mechanisms of action and resistance to TAK-007 utilizing (including but not limited to) quantitative and phenotypic evaluation of immune cells and cellular product characteristics, as well as HLA and KIR characterization.
- Assessment of circulating tumor DNA (ctDNA).
- Assessment of standardized uptake value, metabolic tumor volume, tumor volume computed tomography (CT)/magnetic resonance imaging (MRI), volumetric tumor assessment, and total lesion glycolysis assessed by ^{18}F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) and volumetric tumor assessments by CT/MRI.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This phase 2, open-label, multicenter study will investigate the safety and efficacy of TAK-007 administered intravenously (IV) in adult patients with r/r B-cell NHL, including LBCL patients who have failed ≥2 prior systemic therapies (ie, third or higher line [3L+] treatment) and iNHL patients who have failed ≥2 prior systemic therapies (3L+). Eligible patients are required to have previously received an anti-CD20 monoclonal antibody (mAb) and chemotherapy regimen.

At the beginning of the study, the dose escalation phase will be conducted to assess the acute safety profile, CK, and pharmacodynamics of the TAK-007 cell product at 2 dose levels (200×10^6 [±30%] and 800×10^6 [±25%] CD19 CAR^+ viable NK cells per patient). Previous clinical experience with CD19 CAR NK cells suggests that both proposed dose levels are likely to be clinically active (Liu et al. 2020). A sequential dose escalation guided by Bayesian Optimal Interval (BOIN) design (Liu and Yuan 2015; Yuan et al. 2016; Zhou et al. 2018) will be used (see additional details in Appendix N), followed by expansion cohorts to select the RP2D.

During the dose escalation, only patients who received TAK-007 will be considered as dose-limiting toxicity (DLT)-evaluable. Each dose level will enroll at least 3 patients. The target toxicity rate for the maximum tolerated dose (MTD) is $\phi = 0.25$, and the maximum sample size is 12 total patients for dose escalation. As shown in Table 6.a, the BOIN design uses the following rule to guide dose escalation/ de-escalation:

- If the observed DLT rate at the current dose is ≤0.197, 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 >0.298, 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 12 is reached, or until the number of evaluable patients treated at the current dose reaches 6 and the decision according to above is to stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if Pr(p_j>0.25 |data) >0.95 and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j, j = 1, 2.

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

Number of Evaluable Patients Treated at Current Dose	**1**	**2**	**3**	**4**	**5**	**6**
Escalate if # of DLT ≤	0	0	0	0	0	1
De-escalate if # of DLT ≥	1	1	1	2	2	2
Eliminate if # of DLT ≥	NA	NA	3	3	3	4

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity.
"# 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.

Enrollment into the lower dose level may be continued during exploration of the higher dose level in the dose escalation phase if deemed appropriate by the sponsor and the investigators. In this case, if additional DLTs are identified when additional patients are enrolling, the dose escalation decision will be re-examined using the cumulative DLT rate at this dose level.

Separate expansion cohorts for LBCL and iNHL (Cohorts 1 [LBCL 3L+] and 2 [iNHL 3L+]), with approximately 15 patients each may be initiated for dose level(s) selected based on the dose escalation part, to further evaluate the safety, tolerability, efficacy, and CK and to allow the selection of the RP2D to be used in the rest of the study.

During dose escalation, a 21-day observation period will be placed between the first and the second patient in each dose level, in addition to a 28-day interval between the 2 dose cohorts to allow for DLT assessment.

The sponsor and investigators will select the RP2D for subsequent studies. The decision for RP2D will be based on a review of the preliminary safety and efficacy data during the dose escalation and expansion phase.

The study consists of 5 phases: screening, conditioning (lymphodepleting chemotherapy), treatment and primary follow-up (safety and efficacy when patients have had the opportunity to be evaluated for at least 6 months after TAK-007 administration), secondary follow-up (safety and efficacy evaluations for an additional 18 months), and, at the end of 2 years, a long-term follow up phase for up to 13 additional years. The total duration that an individual patient will participate in this study is 15 years following TAK-007 administration.

Eligible patients will receive lymphodepleting chemotherapy on Days -5, -4, and -3, before receiving a single IV administration of TAK-007 on Day 0.

After TAK-007 administration, response will be assessed locally by CT and/or FDG-PET according to Lugano classification (Appendix D) at Months 1, 3, and 6. Clinical evaluations and laboratory studies will be performed on Days 1, 3, and 7 after TAK-007 administration. Clinical evaluation and laboratory studies will be further performed on Days 10, 14, 21, and 28; followed by Months 2, 3, 4, and 6, depending on how the patient responds to the treatment.

Safety Evaluations

Safety evaluations will include the incidence of AEs, severity and type of AEs, electrocardiograms (ECGs), and changes from baseline in the patient's vital signs and clinical laboratory results at the time points noted in the Schedule of Events (SOE) (Appendix A Table A 1). Additional details regarding the scope and timing of AE monitoring are provided in Section 9.4.13 and Section 10.3, respectively.

Toxicity grading and management will be conducted as follows:

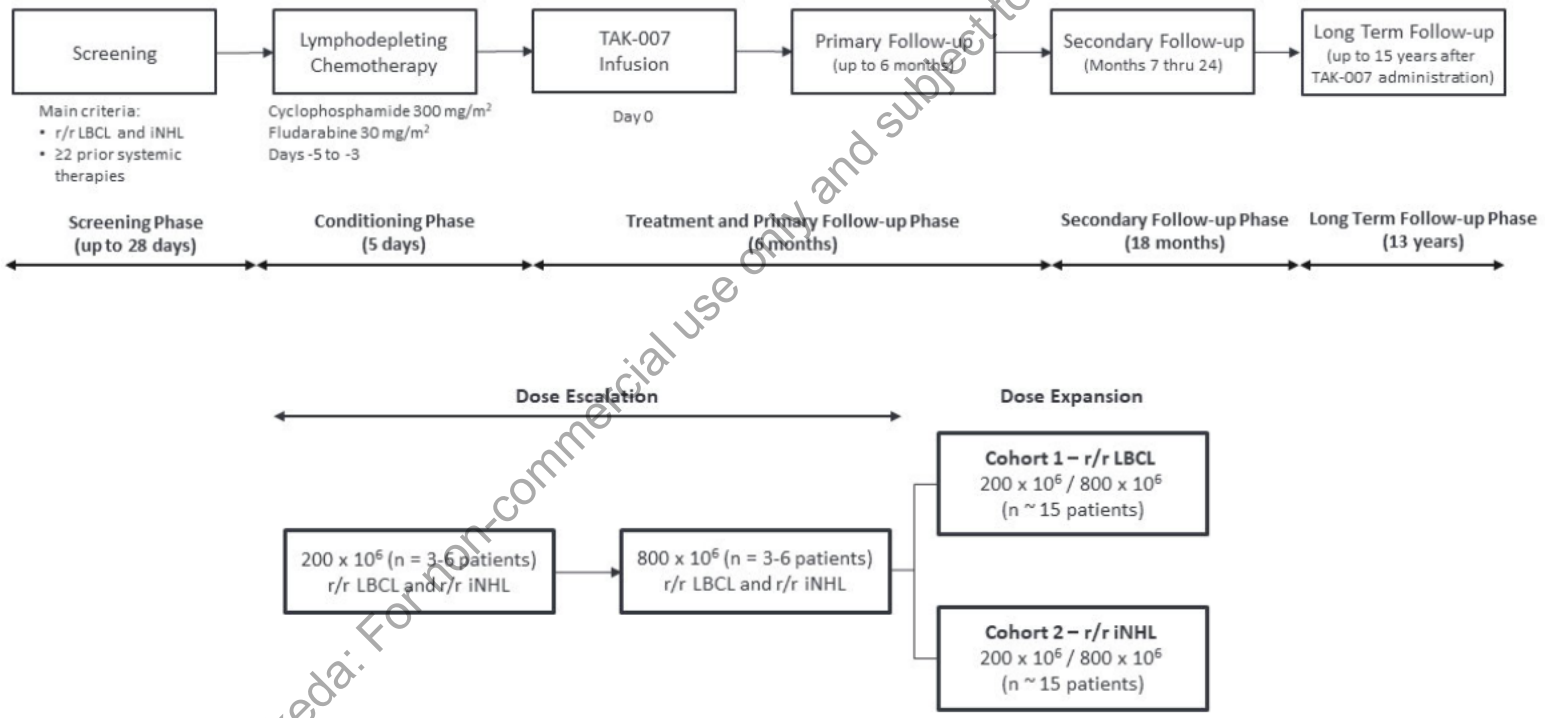
- For most AEs, toxicity grades will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI 2017).
- Grading of CRS and ICANS will be performed following the definitions provided in the ASTCT consensus (Lee et al. 2019) (Appendix G and Appendix H).
- Grading of acute cell-therapy-associated GvHD will follow recommendations by the Mount Sinai Acute GvHD International Consortium (Harris et al. 2016), and grading of chronic cell-therapy-associated GvHD will follow recommendations by the 2014 National Institutes of Health (NIH) Consensus Conference (Jagasia et al. 2015) (Appendix I to Appendix M).
- Management of other immune effector cell therapy-related toxicities (not including CRS, ICANS, or GvHD) will follow CARTOX recommendations (Appendix O).

For each set of grading criteria, a higher (later) version of the criteria may be applied.

Patients who complete study treatment will continue to have follow-up visits for 6 months (Section 9.10). After 6 months, an abbreviated follow-up assessment schedule will be used (Appendix A Table A 3).

The overall study schema for TAK-007-2001 is illustrated in Figure 6.a.

Figure 6.a Study Schematic for TAK-007-2001 Protocol



1

iNHL: indolent non-Hodgkin lymphoma; LBCL: large B-cell lymphoma; r/r: relapsed or refractory.

6.2 Number of Patients

The expected total number of patients to be enrolled in the study is approximately 42 patients in the dose escalation and expansion phase.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-007 and be followed for approximately 2 years in the core study and will then enter the long-term follow-up (LTFU) phase for safety assessments for up to 13 additional years for a total of 15 years after TAK-007 administration per recommendation for genetically modified cell therapy products.

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 response and safety at least 6 months after TAK-007 administration. The data cutoff for final analysis for the CSR addendum will be conducted after all dosed patients have had the opportunity to complete LFTU or if the study has been terminated by the sponsor. EOS is defined as either the date of the last visit of the last patient, or 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 Time Frames for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary Endpoint:		
Incidence of AEs and clinically significant laboratory values and vital signs		Up to 24 months
Secondary Endpoints:		
ORR per investigator	CR + PR as best response to treatment per the Lugano criteria (Appendix D) after TAK-007 administration	Up to 6 months
CR per investigator	Incidence of CR as best response to treatment per the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Appendix D) after TAK-007 administration	Up to 6 months
DOR per investigator	Only for patients who experience an objective response and is the time from the date of first objective response to disease progression per Lugano classification (Appendix D) or death, whichever comes first	Up to 6 months
PFS per investigator	Time from enrollment date to the date of disease progression per Lugano classification (Appendix D) or death from any cause, whichever comes first	Up to 6 months
OS	Time from enrollment to the date of death from any cause	Up to 24 months

CK parameters	• Parameters determined using non-compartmental pharmacokinetic analysis.
	  • C_{max}
	  • t_{max}
	  • t_{last}
	  • AUC_{last}
		Up to 24 months

CK parameters	• Additionally, periodic blood samples are planned to determine TAK-007 levels using a validated ddPCR.	Up to 15 years post-dose

Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Safety and pharmacodynamic biomarkers	Concentration of IL-15 and soluble immune factors (eg, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα, GM-CSF) in plasma over time B cell quantification over time	Up to 6 months
Prevalence and incidence of antidrug antibodies (ie, anti-HLA, anti-CAR)	Percent of patients with detectable anti-HLA and anti-CAR antibodies over time Prevalence – before TAK-007 administration Incidence – after TAK-007 administration	Up to 12 months Dependent on previous testing
Prevalence and incidence of RCR positive test results	Percent of patients with positive RCR test results over time Prevalence – before TAK-007 administration Incidence – after TAK-007 administration	Up to 60 [a] months

AE: adverse event; AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; CAR: chimeric antigen receptor; CK: cellular kinetic(s); C_{max}: last measurable concentration; CR: complete response; CR: complete response; DOR: duration of response; GM-CSF: granulocyte-macrophage colony-stimulating factor; HLA: human leukocyte antigen; IFN: interferon; IL-: interleukin; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RCR: replication competent retrovirus; SOE: Schedule of Events; t_{last}: time of last measurable concentration above the lower limit of normal; t_{max}: time of first occurrence of C_{max}; TNFα: tumor necrosis factor alpha.

[a] Additionally, periodic blood samples are planned for up to 15 years post-dose to determine TAK-007 transgene levels, RCR testing, and immunogenicity assessment (See SOE, Table A 3).

6.3.4 Total Study Duration

The estimated time frame for ~~study~~ completion of primary and secondary follow-up is 5 years including approximately 3 years enrollment and 2-year follow-up.

Patients completing the study follow-up through 2 years will continue in LTFU for up to 13 additional years, for a total of up to 15 years.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Patients aged ≥18 years or meeting country definition of adult, whichever is older, at the time of signing the informed consent.
2. Patients who have a life expectancy ≥12 weeks.
3. Patients who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix E).
4. Patients with a diagnosis of previously treated, r/r histologically proven CD19 expressing disease of the following types:
   a. LBCL, including the following subtypes defined by the WHO:
      i. DLBCL NOS.
      ii. HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangement.
      iii. HGBL NOS without translocations.
      iv. DLBCL arising from iNHL including FL or MZL.
      v. T-cell/histiocyte-rich LBCL.
      vi. DLBCL associated with chronic inflammation.
      vii. Epstein-Barr virus–positive DLBCL-NOS.
      viii. Primary cutaneous DLBCL, leg type.
      ix. PMBCL.
      x. FL Grade 3B.
   b. iNHL, including the following subtypes defined by the WHO:
      i. FL Grades 1, 2, 3A.
      ii. MZL (nodal, extranodal, and splenic).
5. Patients who have measurable disease, defined as at least 1 lesion per the Lugano classification (Appendix D). Lesions situated in a previously irradiated area are considered measurable if radiographic progression has been documented in such lesions following completion of radiation therapy. LBCL should have positron emission tomography (PET)-positive disease per the Lugano classification (Appendix D).

6. Patients who have r/r LBCL or r/r iNHL after ≥2 prior lines of systemic therapy (Expansion Cohorts 1 [LBCL 3L+], and 2 [iNHL 3L +]):
   a. Patients with r/r LBCL must have received an anti-CD20 mAb and an anthracycline-containing chemotherapy regimen and failed or be ineligible for high-dose chemotherapy and ASCT.
   b. Patients with iNHL must have received an anti-CD20 mAb and an alkylating agent (eg, bendamustine or cyclophosphamide).
   c. Preinduction salvage chemotherapy and ASCT should be considered 1 line of therapy.
   d. Any consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 line of therapy with the preceding combination therapy. Maintenance antibody therapy should not be considered a line of therapy.
   e. Single-agent anti-CD20 mAb therapy should not be considered a line of therapy.
   f. Bridging chemotherapy given just prior to CAR-T cell therapy treatment should be considered one line of therapy together with cell therapy.
   g. Patients who have received prior CD19-targeting CAR-T cell therapy must have achieved at least a partial response to the most recent CD19-targeting CAR-T cell therapy.
7. Patients who have adequate bone marrow function defined as follows:
   a. Absolute neutrophil count >500/μL.
   b. Platelet count of >50,000/μL at screening. Patients with transfusion-dependent thrombocytopenia are excluded.
8. Patients who have adequate renal, hepatic, cardiac, and pulmonary function as defined in the study protocol:
   a. Estimated glomerular filtration rate (GFR; Modification of Diet in Renal Disease [MDRD] equation) ≥30 mL/min.
   b. Serum alanine aminotransferase/aspartate aminotransferase ≤5 times the upper limit of normal range (ULN), as long as patient is asymptomatic.
   c. Total bilirubin ≤2 mg/dL. Patients with Gilbert's syndrome may have a bilirubin level >2 × ULN, per discussion between the investigator and the medical monitor.
   d. Left ventricular ejection fraction (LVEF) ≥40% as determined by an echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed within 1 month of determination of eligibility.
   e. No evidence of clinically relevant pericardial effusion, and no acute clinically significant ECG findings.
   f. Absence of Grade ≥2 pleural effusion. Grade 1 stable pleural effusions are allowed.

g. Baseline oxygen saturation >92% on room air.

9. Patients are required to consent to provide either sufficient archived formalin-fixed paraffin embedded (at least 10 unstained slides, ideally 20 unstained slides) or fresh tumor tissue obtained after the last relapse (see laboratory manual for details). Exception may be granted by sponsor medical monitor per discussion with investigator.
10. 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 TAK-007 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, or
    e. Agree not to breastfeed a baby or donate an egg or eggs (ova) during the study and until at least 12 months following TAK-007 administration.
11. 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 TAK-007 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, or
    c. Agree not to donate sperm during the study and at least until 12 months following TAK-007 administration.
12. Patients must give 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.
13. Patients who have the willingness and ability to comply with scheduled visits and study procedures.

7.2 Exclusion Criteria

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

1. Patients with total body weight of <40 kg.
2. Patients with primary or secondary central nervous system (CNS) involvement by lymphoma. Patients with a history of secondary CNS involvement by lymphoma without evidence of CNS involvement at screening may be included.
3. Patients with Burkitt lymphoma, mantle cell lymphoma, lymphoplasmocytic lymphoma, or transformation from CLL/small lymphocytic lymphoma (Richter transformation).
4. Patients with a history of malignancy other than nonmelanoma skin cancer, carcinoma in situ (eg, cervix, bladder, breast), low-grade tumors deemed to be cured and not treated with systemic therapy (eg, by gastro-endoscopy curatively removed gastric cancer) or unless disease free for ≥3 years at screening.
5. Patients who have undergone autologous or allogeneic transplant or CAR-T or CAR-NK cell therapy within 3 months of planned enrollment. Patients after allogeneic transplant have to be off systemic immunosuppressive therapy and without the evidence of clinically relevant acute or chronic GvHD at the time of enrollment.
6. Treatment with any investigational products or any systemic anticancer treatment within 14 days or 2 half-lives of the treatment (whichever is longer) before conditioning therapy. For rituximab, a half-life of 22 days should be considered.
7. Patients with active infection, including fungal, bacterial, viral, or other infection that is uncontrolled or requires IV antimicrobials for management within 3 days before enrollment.
8. Patients with active HIV, HBV, or HCV infection at screening (positive DNA/RNA test).
9. Patients with a history or presence of active or 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.
10. Patients with any of the following within 6 months of enrollment: myocardial infarction, cardiac angioplasty or stenting, unstable angina, symptomatic congestive heart failure (ie, New York Heart Association Class II or greater), clinically significant arrythmia (including uncontrolled atrial fibrillation), or any other clinically significant cardiac disease.
11. Patients with a history of autoimmune disease or solid organ transplantation, requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years.
12. Patients who have received a live vaccine ≤6 weeks before the start of the conditioning regimen.
13. Patients with admission or evidence of current illicit drug use, drug abuse, or alcohol abuse.

14. Patients with ~~the~~ history of severe immediate hypersensitivity reaction to any of the agents used in this study, including cyclophosphamide and fludarabine.
15. Female patients who are lactating and breastfeeding.
16. Female patients who have a positive serum pregnancy test.
17. Patients with any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

8.0 STUDY DRUG

The TAK-007 investigational product will be provided as a cryopreserved suspension of living cells that will be thawed by clinical staff immediately before administration. The doses of TAK-007 are 200×10^6 (±30%) and 800×10^6 (±25%) CD19 CAR^+ viable NK cells per patient.

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

If an enrolled patient becomes ineligible to receive TAK-007 due to development of medical complications, such as systemic infection, sepsis, hemodynamic instability, or altered mental status during/immediately after lymphodepleting chemotherapy but before TAK-007 administration, the administration of TAK-007 may be delayed for up to 7 days on investigator's decision. Any dose that requires >7 days delay should result in discontinuation of the patient from TAK-007 treatment. Day 0 will be defined as the actual day of TAK-007 administration after lymphodepleting chemotherapy. In addition, the investigator is required to consult with the sponsor medical monitor in case of delayed TAK-007 administration.

TAK-007 administration will follow lymphodepleting chemotherapy (fludarabine 30 mg/m^2 body surface area [BSA] per day IV on Days -5, -4, and -3 and cyclophosphamide 300 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 the first TAK-007 administration.

The outpatient setting is preferred for the administration of TAK-007.

The instructions for administration of lymphodepleting chemotherapy are outlined in the cell handling manual. Details for handling (eg, shipping, receipt, thaw) and administration of TAK-007 are contained in the cell handling manual.

8.2 Prohibited Concomitant Medications and Procedures

The following medications are prohibited during the treatment (starting from the signed informed consent) and primary follow-up phase (6 months after TAK-007 administration) unless there is considerable medical need or approval per sponsor's medical monitor:

- Administration of systemic steroids and other immunosuppressant drugs is strictly forbidden 48 hours before, during, or after any TAK-007 administration unless required for physiologic

replacement (up to 35 mg/day of hydrocortisone equivalent) or for the treatment of a critical medical condition, or progression of disease following TAK-007. Recent or current use of inhaled or topical steroids is not exclusionary.

- Granulocyte colony-stimulating factors (G-CSF) for 7 days after the first TAK-007 administration.
- Granulocyte macrophage colony-stimulating factors.
- Live vaccines.
- Other systemic antilymphoma therapies, including but not limited to venetoclax, rituximab, and lenalidomide, are prohibited before disease progression.

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 TAK-007, except the prohibited concomitant medications, is allowed. The patient must be told to notify the investigational site about any new medications taken after TAK-007 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.

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 primary follow-up phase of the study without consultation with the investigator.

8.4 Precautions and Restrictions

Considering potential CAR-related toxicities (See Section 8.5), appropriate safety measures should be taken when treating patients with TAK-007. Assessment and grading of CRS and ICANS will be performed following the definition provided in the ASTCT consensus (Lee et al. 2019) [Appendix G and Appendix H]. Toxicity management will follow the recommendation of the CARTOX Working Group (Appendix O) or be performed according to institutional guidelines. Other recommended mitigation strategies for each of the potential risks are provided in the study manual or equivalent.

It is not known what effects TAK-007 has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or impregnating a partner for 1 year after the dose of TAK-007. Patients who are able to become pregnant or impregnate a partner 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 F):

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to one of the following:
  - 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, or
  - Agree not to breastfeed a baby or donate an egg or eggs (ova) during the study and until at least 12 months following TAK-007 administration.

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

- Agree to practice effective barrier contraception with partners who can become pregnant 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 with partners who can become pregnant, 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, or
- Agree not to donate sperm during the study and at least until 12 months following TAK-007 administration.

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

8.5 Management and Mitigation of AEs Associated With CAR Cell Therapy

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

Table 8.a CAR-T Toxicity Assessment and Management Guidelines

Toxicity	Monitoring, Assessment, and Management Guidelines
CRS	• Close monitoring of patients during and after TAK-007 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 TAK-007 administration according to the study protocol. • Monitoring for PML according to PML diagnostic criteria, and monitoring for other neurotoxicities according to 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 TAK-007 administration according to the study protocol. • If any Grade ≥2 acute GvHD is observed after administration of TAK-007 drug product exceeding 1.3×10^6 residual T-cells per single high dose of 800×10^6 CAR^+ NK cells, the following actions will be taken: – All batches with $>1.3 \times 10^6$ total residual T cells per single high dose of 800×10^6 CAR+ NK cells, will be immediately quarantined. – The batch release acceptance criterion of residual T cells will be revised to $\leq 1.3 \times 10^6$ T cells per single high dose of 800×10^6 CAR^+ NK cells to ensure that the total residual T cell remain below 4.0×10^6 for the entire three dose regimen. – For any batch that is $>1.3 \times 10^6$ T cells per single high dose of 800×10^6 CAR^+ NK cells, the sponsor may release a dose on an individual patient basis after confirmation that the total CD3+ T cells from three doses meets the criterion of $\leq 1.0 \times 10^5$/kg body weight. • 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 Immune Effector Cell Therapy Toxicity Assessment and Management (also known as CARTOX).
TLS	• Close monitoring before and after lymphodepleting chemotherapy and TAK-007 administration according to study protocol. • For patients who are at an increased risk of TLS, hydration and prophylactic treatment should be provided. TLS events should be treated aggressively.
Hypersensitivity and IRRs	• Close monitoring of patients for symptoms of hypersensitivity or IRRs during and after administration of TAK-007 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.

Table 8.a CAR-T Toxicity Assessment and Management Guidelines

Toxicity	Monitoring, Assessment, and Management Guidelines
Generation of RCR and risk of second primary malignancy	• Monitoring for development of any second primary malignancies. • Adherence to FDA Guidance on Long-Term Follow-Up After Administration of Human Gene Therapy Products (FDA 2018). Takeda will implement a LTFU phase to further assess the long-term risk profile of TAK-007 therapy; study participants will be followed for up to 15 years. • Monitoring for clonality according to the study protocol (Section 9.4.19.1, Appendix A). • Monitoring for RCR positivity according to study protocol.
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; CAR: chimeric antigen receptor; CARTOX: CAR-T–cell therapy–associated TOXicity; CRS: cytokine release syndrome; FDA, Food and Drug Administration; 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; LTFU: long-term follow-up; PML: progressive multifocal leukoencephalopathy; RCR: replication competent retrovirus; TLS: tumor lysis syndrome.

As an additional risk mitigation measure, patients will be required to carry a patient emergency card detailing treatment site and investigator contact information, clinical study information, and a back-up 24-hour emergency number for 6 months after TAK-007 administration. 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.

8.6 Definition of DLTs

DLTs are defined as events occurring during the Dose Escalation phase of this study, that meet the criteria below that occur by Day 28 after administration of TAK-007 infusion (Day 0).

1. Nonhematologic treatment-emergent adverse events (TEAEs) Grade ≥3 clearly unrelated to the underlying disease and at least possibly related to the investigational therapy (TAK-007 and/or lymphodepletion) will be considered DLTs with the following exceptions:
   - Asymptomatic laboratory changes (other than renal and hepatic laboratory values) that can be successfully managed (reversal of Grade 4 events to Grade ≤2; reversal of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
   - Grade 3 nausea/vomiting that can be managed subsequently with antiemetics (Grade 3 nausea or vomiting that persists beyond 72 hours with or without appropriate medical intervention will be considered a DLT).
   - Grade 3 fatigue lasting <7 days.
   - Grade 3 diarrhea lasting <72 hours.
   - Grade 3 renal and hepatic toxicity that improves to Grade ≤2 within 7 days.
   - Grade 3 IRR that responds to symptomatic treatment, without recurrence of Grade 3 symptoms.
   - Grade 3 TLS lasting ≤14 days and Grade 4 TLS lasting ≤7 days.
2. Hematologic TEAEs Grade ≥3 that are clearly not attributable to previous lymphoma therapy, and/or marrow infiltration related to the underlying disease, and at least possibly related to the investigational therapy (TAK-007 and/or lymphodepletion) will be considered DLTs with the following exceptions:
   - Grade ≥3 neutropenia lasting <21 consecutive days.
   - Grade 3 febrile neutropenia lasting <14 days.
   - Grade ≥3 thrombocytopenia lasting <21 consecutive days.
   - Cytopenia except neutropenia and thrombocytopenia as described above.
3. Acute GvHD Grade 2 requiring systemic steroids and not resolving within 7 days.

8.7 Enrollment Pausing Criteria

Enrollment will be paused and investigators and health authorities notified if any of the following events occur:

- Death suspected to be at least possibly related to TAK-007 therapy.
- Life-threatening (Grade 4) toxicity that is unmanageable and unrelated to chemotherapy or underlying disease, and at least possibly related to the investigational therapy (TAK-007 therapy).

- Occurrence of two Grade 4 DLTs in 2 patients at the lower dose level during the Dose Escalation phase, that are at least possibly related to the investigational therapy (TAK-007 and/or lymphodepletion).
- Oligoclonal or monoclonal CAR-NK cell proliferation beyond 6 months from TAK-007 cell product administration.
- Detectable RCR after TAK-007 administration.

If a higher than expected incidence of Grade ≥3 neurotoxicity or Grade ≥3 CRS is observed (incidence threshold defined as >33% incidence after at least 6 patients have been administered TAK-007), then the following events will be considered additional enrollment pausing criteria:

- Grade ≥3 neurotoxicity event.
- Grade 4 CRS event.
- Grade 3 CRS that lasts >72 hours with no improvement to a lower grade.

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.

The study may be halted if 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 sponsor decides to discontinue the development of TAK-007.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of TAK-007

TAK-007 is an unrelated, HLA-agnostic (not selected based on recipient HLA genotype), allogeneic donor umbilical CB-derived SFG.iCas9.2A.CAR.CD19-28-3zeta.2A.IL15 transduced NK cell product.

8.10 Preparation

TAK-007 should be prepared in accordance with the cell handling manual.

Management and premedication for cryopreserved product administration is per institutional practice, including acetaminophen/paracetamol and an H1 antihistamine. Premedication may be based on patient risk of hypersensitivity reactions and IRRs. Steroids should not be used for premedication.

Toxicities potentially associated with the administration of TAK-007 (containing dimethylsulfoxide [DMSO]) include changes in heart rate or heart rhythm, chest tightness, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping,

fluid overload, headache, dyspnea, presence of DMSO taste and odor, hemoglobinuria, allergic reaction, and acute renal failure. These toxicities are unlikely.

If the patient develops a medical condition including, but not limited to, infection, fever, sepsis, hypotension, or cardiac arrhythmia during/immediately after lymphodepleting chemotherapy but before TAK-007 administration, TAK-007 administration may be delayed for up to 7 days on investigator's decision (Section 8.1). Medical management will be provided per institutional guidelines. Decision to administer the drug in this setting will be made in consultation with the sponsor's medical monitor.

TAK-007 will be shipped to the clinical site in a proper container that can maintain and control the cryopreserved condition.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

The final product will be shipped to the clinical site as 1 dose of cryopreserved cells at appropriate concentration for administration without further manipulation. Trained medical staff will thaw the product using appropriate equipment and administer the product intravenously to the patients.

Refer to the cell handling manual for details.

8.11 Packaging and Labeling

Product packaging should include the product label, which includes dose information (number of CAR^+ NK cells), 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 -140°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 Fludarabine

The purine antagonist antimetabolite fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose.

8.13.2 Cyclophosphamide

The nitrogen mustard-derivative cyclophosphamide possesses potent immunosuppressive activity. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent.

9.0 STUDY CONDUCT

This study 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.

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 institutional review board (IRB)/independent ethics committee (IEC).

9.3 Treatment Group Assignments

Patients will be enrolled in dose escalation cohorts followed by expansion cohorts, as outlined below:

Dose Escalation cohorts: Eligible patients will be assigned to receive lymphodepleting chemotherapy consisting of IV fludarabine (30 mg/m^2 body surface area [BSA] per day) and cyclophosphamide (300 mg/m^2 BSA per day) on Days -5, -4, and -3 before a single IV administration of TAK-007 at a dose of 200 × 10^6 (±30%) or 800 × 10^6 (±25%) CD19 CAR$^+$ viable NK cells on Day 0.

Dose Expansion Cohort 1 (LBCL 3L+) and Cohort 2 (iNHL 3L+): Eligible patients will be assigned to receive a single IV administration of TAK-007 at a dose of 200 × 10^6 (±30%) or 800 × 10^6 (±25%) CAR+ viable NK cells on Day 0 of the study.

9.4 Study Procedures

Refer to the SOE (Appendix A Table A 1) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Screening Phase (Day -33 to Day -6)

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 28 days before lymphodepleting chemotherapy.

Screening tests will include:

Evaluation of eligibility criteria, disease assessment, and collection of tumor tissue:

- Patients are required to consent to provide either archived diagnostic formalin-fixed paraffin embedded tumor tissue from a sample obtained after the last lymphoma treatment or a pretreatment fresh tumor biopsy to perform tumor and microenvironment assessments, including but not limited to immunohistochemistry; this requirement may be waived at the discretion of the sponsor. Central confirmation of diagnosis and CD19 expression is not mandatory for enrollment.
- 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 E).
- Disease assessment per Lugano criteria (Appendix D) including: FDG-PET and/or contrast-enhanced CT of neck, chest, abdomen, and pelvis (contrast in CT may be replaced by MRI in patients with contraindication).
- Lymph node evaluation (aspiration/biopsy, as clinically indicated): immunohistochemistry, flow cytometry, morphology, and molecular studies.
- Bone marrow (aspiration/biopsy): immunohistochemistry, flow cytometry, morphology, and molecular studies. Archived bone marrow biopsy sample (and assessment) within 42 days before the start of lymphodepleting chemotherapy is acceptable if no antitumor therapy was given after bone marrow evaluation. Bone marrow biopsy assessment will be performed locally.
- Assessment of physiologic reserves including: 12-lead ECG, ECHO or MUGA scan for ejection fraction, and pulse oximetry on room air.
- Infectious disease tests (according to institutional guidelines) to include at a minimum: serology tests for CMV, HIV-1, HBV, and HCV.

Patients should not be enrolled if they are unwilling to participate in the secondary follow-up phase (through Month 24) and the LTFU phase (through Year 15) of this study.

- Each patient will be informed of the purpose and duration of the LTFU phase, including time intervals, schedule of visits (or contact), and details as to what those contacts will involve.

TAK-007 administration should occur within 6 weeks of written informed consent.

- 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.

Enrollment is defined as the time when a patient meets the eligibility criteria during the screening phase and is registered in the study. If at any time the patient fails to meet the eligibility criteria during the screening phase, the patient should be designated as a screen failure on the patient screening log with the reasons for failing screening. Screen failures will be captured and tracked in the interactive response technology and electronic data capture (EDC).

Procedures and assessments to be conducted during the screening phase are shown in the SOE (Appendix A Table A 1).

Patients who fail to meet the eligibility criteria will be allowed to be rescreened once. Patients will undergo the assessment that initially resulted in the patient failing screening including any other procedures that fell outside of the designated screening window (eg, laboratory assessments).

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 the first TAK-007 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 TAK-007 to the study site will be confirmed by the sponsor before start of lymphodepleting chemotherapy. For details, see the cell handling manual.

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

During the conditioning phase:

- The outpatient setting is preferred for the application of lymphodepleting chemotherapy.
- 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 given expected duration of immunosuppression after administration of lymphodepleting chemotherapy and should be continued for a minimum of 3 months after TAK-007 administration. *Pneumocystis jiroveci* pneumonia (cotrimoxazole) prophylaxis is recommended for 6 months after TAK-007 administration.
- Lymphodepleting chemotherapy administration includes:
  - Fludarabine 30 mg/m^2 BSA per day will be 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 fludarabine. The MDRD formula should be used to calculate GFR.

In the event of fludarabine shortage, the actual dose administered may be rounded down, as long as the actual dose is within 10% of the calculated dose. Every attempt must be made to secure the full dose of fludarabine.

– Cyclophosphamide 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 has to be at least 2 chemotherapy-free days between the last day of lymphodepleting chemotherapy and TAK-007 administration.

Procedures and assessments to be conducted during the conditioning phase are shown in the SOE (Appendix A Table A 1). Patients should not experience significant change in clinical status compared with initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of AEs associated with experimental cell infusion.

9.4.3 Treatment and Follow-up Phases (Day 0 to Month 24)

The treatment and follow-up phases begin with TAK-007 administration on Day 0 and continue up to Month 24.

- Primary follow-up analysis period: up to 6 months after TAK-007 administration of the last patient enrolled in the study.
- Secondary follow-up analysis period: up to 24 months after TAK-007 administration of the last patient enrolled in the study.

After 24 months, patients will be followed within the LTFU phase for up to 13 additional years, for a total duration of up to 15 years following TAK-007 administration.

Patients must not experience significant deterioration following lymphodepleting chemotherapy and before treatment with TAK-007. Refer to Section 8.10 and Section 8.1 for a description of TAK-007 preparation and administration procedures.

Day 0: On Day 0, TAK-007 will be administered IV. Premedication may include acetaminophen and an H1-antihistamine according to institutional standards for DMSO-containing cell therapy products. Premedication may be based on the patient's risk of hypersensitivity reactions and IRRs. The use of 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 TAK-007 delivery, TAK-007 administration may be delayed for up to 7 days (Section 8.1). There has to be at least 2 chemotherapy-free days between the last day of lymphodepleting chemotherapy and the first

TAK-007 administration. In case of delayed TAK-007 administration, Day 0 will be defined as the day of actual TAK-007 administration.

The outpatient setting is preferred for the administration of TAK-007.

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 each TAK-007 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 TAK-007 administration.
- 1.5, 2, and 3 hours (±10 minutes) after start of TAK-007 administration.

Day +1 to Month 24: Following TAK-007 administration, all patients will be followed to at least Month 24 during the secondary follow-up phase of the study. Posttreatment evaluations will be conducted during the treatment and follow-up phases as shown in the SOE (Appendix A Table A 1 for the period up to 6 months and Appendix A, Table A 3 for the period after 6 months, including secondary follow up and LTFU).

The outpatient setting for assessments in the first week following TAK-007 dose administration is recommended. Evaluations may be withheld if the treating physician feels that there is a strong contraindication to perform the study assessments (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, Table A 1).

Transfusion Support

Following initiation of the lymphodepleting chemotherapy, all blood products for transfusion, with the exception of TAK-007, 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 LTFU Phase (Ongoing – up to Year 15 Following TAK-007 Administration)

Upon implementation of Protocol Amendment 5, the LTFU phase will begin for all patients who have completed the 2-year secondary follow-up and will continue for up to 15 years after TAK-007 administration.

The SOEs for this LTFU phase is provided in Appendix A, Table A 3.

Collection of LTFU data may commence with a site-based approach if the patient continues follow up at the same site where TAK-007 treatment was administered. It is possible that over time, there may be a transition to a centralized approach where a research coordinating center may serve as a central site and manage subsequent LTFU data collection.

The purpose of LTFU is to identify and mitigate the long-term risks of TAK-007 treatment and to understand the persistence of TAK-007 in patients after treatment.

After 2 years on study and up to 15 years after administration of TAK-007, relevant patient histories should be collected at least once a year to document the following:

- Unexpected illnesses and hospitalizations:
  - The focus should be on new incidences of infections (including opportunistic pathogens), new hematological disorders, new incidences or exacerbations of prior neurological, rheumatological, or autoimmune disorders, and new malignancies. (See Section 10.3 for additional details)
  - Appropriate follow-up for the events listed above must be conducted and recorded in order to assess whether the event is associated with TAK-007 treatment.
  - Investigators should consider CK DNA and/or RCR testing of clinical samples, if appropriate.
- Subsequent cancer therapies and exposures to mutagenic agents.
- Results of any ongoing testing per protocol (eg, blood for CK DNA and RCR testing).

9.4.4.1 RCR Testing

If all post-treatment RCR samples are negative for the first year or after 2 negative consecutive tests (which ever comes later), collection of samples may be discontinued in that patient. However, if a previously RCR-negative patient develops an AE suggestive of retrovirus-associated disease (ie, new malignancy, new or significant exacerbations of neurological diseases or hematological diseases), relevant clinical samples should be collected and tested for RCR.

If a positive RCR assay result is obtained, the investigator will be informed, and the patient will be scheduled for a confirmatory RCR retest. If the retest is positive, the result must be submitted as an SAE within the timeline described in Section 10.2 of the protocol. If deemed necessary, a more extensive patient monitoring plan will be developed in consultation with health authorities such as the US Food and Drug Administration (FDA).

9.4.4.2 TAK-007 Persistence

To detect the presence of a transgene in patients, periodic blood samples are planned for up to 15 years post-dose (See Appendix A, Table A 3). These samples will be analyzed using a validated ddPCR assay with adequate sensitivity. Furthermore, additional confirmatory testing may be conducted for samples with detectable transgene prior to confirming those as positive.

9.4.5 Informed Consent

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.

9.4.6 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.

9.4.7 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 9.4.12.

9.4.8 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A Table A 1). Any clinically relevant findings will be documented.

9.4.9 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 Table A 1).

9.4.10 Vital Signs

Vital sign measurements, including (after 3 to 5 minutes in the sitting or supine position) measurements of diastolic and systolic blood pressure, heart rate, and body temperature will be assessed as specified in the SOE. Percutaneous oxygen saturation will also be measured according to the SOE (Appendix A Table A 1).

9.4.11 Pregnancy Test

A serum pregnancy test will be performed for all women of childbearing potential at screening. Urine pregnancy tests are allowed for the rest of the visits. The results must be available and negative before lymphodepleting chemotherapy and treatment with TAK-007. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

9.4.12 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 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.

9.4.13 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE (Appendix A Table A 1) and in Section 10.3. For patients who receive lymphodepleting chemotherapy and do not receive TAK-007, all AEs (regardless of causality) will be collected for the first 30 days following lymphodepleting chemotherapy.

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

9.4.14 Enrollment

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

9.4.15 12-Lead ECGs and ECHO/MUGA Scans

A single 12-lead standard safety ECG will be performed to assess eligibility as specified in the SOE (Appendix A Table A 1). 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 LVEF measured by ECHO or MUGA scan will be performed during screening as indicated in SOE.

9.4.16 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally and will be performed as outlined below.

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a and urine samples for analysis of the parameters will be obtained as specified in the SOE (Appendix A Table A 1).

SARS-CoV-2 testing should be conducted per institutional standards for any suspicion of SARS-CoV-2 infection or known exposure. SARS-CoV-2 testing should follow ASTCT published guidelines for cellular therapy during the COVID-19 pandemic (Bachanova et al. 2020).

Table 9.a Hematology, Clinical Chemistry, and Serum Immunoglobulin Tests

Hematology	Serum Chemistry	Coagulation	Serum Immunoglobulin
Hematocrit	Albumin	aPTT	IgA
Hemoglobin	Alkaline phosphatase	Prothrombin time	IgG
Leukocytes with differential	Alanine aminotransferase	International normalized ratio	IgM
Absolute lymphocyte count	Aspartate aminotransferase		
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		
	β2 microglobulin (only at screening)		

aPTT: activated partial thromboplastin time; eGFR: estimated glomerular filtration rate; Ig: immunoglobulin; MDRD: Modification of Diet in Renal Disease.

Hematology and serum chemistry samples may be taken within the windows specified for each visit according to the SOE (Appendix A, Table A 1), and coagulation testing may be conducted 24 hours before a visit. All results must be evaluated before dosing. On the day of TAK-007 administration, an additional hematology sample will be drawn at 1 hour (±15 minutes) after the start of TAK-007 administration (Appendix A, Table A 1, footnote h).

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, Table A 1). For patients with a medical history of HBV/HCV infection, HBV DNA or HCV RNA must be monitored after TAK-007 administration as described in the SOE (Appendix A, Table A 1). Patients who

are HIV-positive but have a negative viral load at screening must continue to have HIV viral load monitored per institutional guidelines for the duration of the study. Handling of clinical laboratory samples will be outlined in the laboratory manual.

9.4.17 Disease Assessment

Patients will undergo radiographic evaluation consisting of FDG-PET imaging and/or contrast-enhanced CT of neck, chest, abdomen, and pelvis to monitor and assess disease response. In case of contraindications against contrast-enhanced CT, MRI can be used instead. Bone marrow biopsy to confirm CR in the bone marrow will be performed for iNHL patients at the time of radiographic CR and initial bone marrow involvement. Response will be assessed locally using the International Working Group (IWG) 2014 Lugano classification and according to the IWG 2014 Lugano classification (Cheson et al. 2014) (Appendix D).

The disease burden is recorded at baseline and at Months 1, 3, and 6 using FDG-PET and/or contrast-enhanced CT/MRI. An FDG-PET scan extending from the base of the skull through the mid-thighs will be performed at baseline for all patients enrolled to determine FDG avidity. For FDG -avid patients, FDG-PET scans should be acquired additionally at 3 subsequent response assessments (Months 1, 3, and 6). Additional PET assessments should be conducted on FDG-avid patients who did not achieve CR at the abovementioned schedule, and may be used to confirm assessment of CR on CT/MRI, to confirm recurrence or progression of disease, or as clinically indicated per investigator discretion.

Disease assessment will be done using contrast-enhanced CT/MRI at other time points. For patients who are not FDG-avid, disease assessment should be done with contrast-enhanced CT/MRI as per the above imaging schedule. The CT portion of an FDG-PET scan may be used as the source of the CT scan, but the CT scan will need to be of diagnostic quality and contain IV contrast. If the CT portion of the PET scan is not of diagnostic quality, additional contrast-enhanced, diagnostic quality CT/MRI should also be obtained. The same imaging modality should be used consistently throughout the study to monitor the disease status. Disease assessment will be performed for all patients who received TAK-007.

Vaccination against the SARS-CoV-2 virus has been shown to cause transient, reactive adenopathy in about 10% to 15% of patients. Enlarged axillary, cervical, and supraclavicular lymph nodes in the vicinity of drainage areas of sites of vaccine injection have been reported (Lehman et al. 2021; Su et al. 2022), with some of the affected lymph nodes appearing to be PET-avid. It is possible that this phenomenon can mimic cancer-related adenopathy and may have a confounding effect in the interpretation of efficacy among oncology patients undergoing serial follow-up on imaging scans. For this reason, it is not recommended to schedule baseline or follow-up imaging scans within 2 weeks of SARS-CoV-2 vaccination, where possible. If vaccination has already occurred close to the imaging visit, the original disease assessment schedule should be followed, and patient treatment should not be delayed. In the event of confounding findings on imaging that are assessed as likely due to the effects of vaccination, a follow-up scan 8 to 12 weeks after vaccination should be considered.

9.4.18 CK, Immunogenicity, and Biomarker Samples

9.4.18.1 Primary Specimen Collection

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in the SOE (Appendix A Table A 2 and Table A 3) for CK of TAK-007, serum cytokine measurements, and biomarker assessments. On days when lymphodepleting chemotherapy is administered, blood samples should be drawn before dosing. The primary specimen collection is presented in Table 9.b.

Table 9.b Primary Specimen Collection

No.	Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Endpoint
1	Blood sample for CK	Blood	DNA	CK	Secondary
2	Plasma sample for IL-15 and other cytokines	Blood	Plasma	CK, PD, and biomarker measurements	Secondary
3	Blood sample for B cell aplasia and T/B/NK cell counts	Blood	--	Biomarker measurements	Secondary
4	Serum sample for anti-HLA Ab AND anti-CAR immunogenicity testing	Blood	Serum	Humoral immunogenicity evaluation	Secondary
5	Blood sample for RCR testing	Blood	DNA	RCR testing for safety	Secondary
6	Sample for HLA and KIR typing	Blood	DNA	Biomarker measurement	Exploratory
7	Blood sample for flow cytometry (CAR^+ NK enumeration)	Blood	--	Exploratory assay for CK	Exploratory
8	Plasma sample for ctDNA	Blood	Plasma ctDNA, buffy coat DNA	Exploratory ctDNA assessment	Exploratory
9	Blood sample for immunophenotyping	Blood	PBMC	Biomarker measurements	Exploratory
10	Blood sample for cellular immunogenicity	Blood	PBMC	Cellular immunogenicity evaluation	Exploratory
11	Bone marrow aspirate	Bone Marrow	Cells and DNA	CK and immunophenotyping	Exploratory

Table 9.b Primary Specimen Collection

No.	Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Endpoint
12	Fresh tumor tissue biopsy sample a) Excisional or core needle biopsy OR b) LN aspirate	Tumor tissue biopsy, LN and/or BM as clinically indicated	FFPE block (preferred) or FFPE slides (for excisional or core needle biopsy) Cells, DNA (for LN aspirate)	CD19 expression evaluation, biodistribution, biomarker measurements, NGS	Exploratory

Ab: antibody; BM: bone marrow; CAR: chimeric antigen receptor; CK: cellular kinetics; ctDNA: circulating tumor DNA; FFPE: formalin-fixed, paraffin embedded; HLA, human leukocyte antigen; IL-15: interleukin-15; KIR: killer immunoglobulin-like receptor; LDC: lymphodepleting chemotherapy; LN: lymph node; NGS: next-generation sequencing; NK: natural killer; PBMC: peripheral blood mononuclear cell; PD: pharmacodynamics; RCR: replication competent retrovirus.

If required, blood samples collected for secondary endpoints can be used for exploratory endpoint analyses only after final CK analysis has been completed. 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. If under some circumstances of unmet blood collection, the prioritized assessments are listed in Table 9.c.

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

Table 9.c Prioritized Sequence for Specimen Collection

Priority	Primary Specimen	Specimen Name in Schedule of Events (Assessments)
1	Blood	Blood sample for DNA (CK, RCR)
2	Plasma	Plasma sample for pharmacokinetics (IL-15) Plasma sample for cytokines (cytokine panels)
3	Blood	Blood sample for T/B/NK cell counts
4	Serum	Serum sample for anti-HLA Ab testing (humoral immunogenicity) Serum sample for anti-CAR Ab testing (humoral immunogenicity)
5	Blood	Blood sample for HLA and KIR typing Blood sample for flow cytometry (CAR+ NK enumeration)
6	Plasma	Plasma sample for ctDNA
7	Blood	Blood sample for immunophenotyping
8	Blood	Blood sample for cellular immunogenicity

Ab: antibody; CAR: chimeric antigen receptor; CK: cellular kinetics; ctDNA: circulating tumor DNA; HLA, human leukocyte antigen; IL-15: interleukin-15; KIR: killer immunoglobulin-like receptor; NK: natural killer; RCR: replication competent retrovirus.

In addition, patients with CD19 CAR$^+$ allelic frequency >1% of the housekeeping gene control at 6 months from TAK-007 administration will be asked to return for a confirmatory blood test before the next visit within 3 months. If the confirmatory test is positive, then genomic vector integration sites will be determined. If integration site analysis reveals monoclonality or oligoclonality pattern and/or integration at or near an oncogenic locus, this information will be submitted as an information amendment to the IND within 30 days. In addition, a monitoring plan (including follow-up molecular analyses) that is specific for the healthcare risks anticipated, given the nature of the integration site and vector target cell type, will be developed in collaboration among the principal investigator, and according to local regulations.

If no evidence of oligoclonality or monoclonality is observed, a summary of all analyses for the pattern of vector integration sites will be presented in the annual report.

9.4.18.2 Tumor and Bone Marrow Biopsies and Aspirates

Tumor biopsies, according to the treating institution's guidelines, will be obtained at prespecified time points, as outlined in the SOE (Appendix A, Table A 1).

Screening lymph node and/or bone marrow biopsy (archived): An archived tumor biopsy will be tested to assess the expression level of CD19 and other biomarkers in tumor cells. If relevant to initial patient disease assessment, the molecular subtype of the disease will be reviewed. Exploratory biomarker analyses including but not limited to sequencing and immunochemistry will be performed to assess predictive biomarkers, mechanism of action, and mechanism of resistance. A fresh biopsy/aspirate will be required in the absence of archived tissue. Excisional biopsy is preferred over core needle biopsy or fine needle aspirate, unless clinically contraindicated. This requirement may be waived by the study medical monitor.

Posttreatment lymph node and/or bone marrow biopsy (fresh): For patients who sign the optional portion of the consent form, a fresh tumor biopsy (core needle biopsy preferred over fine needle aspirate) and bone marrow aspirate will be collected between Days 7 to 14 to assess tissue concentration and mechanism of action of TAK-007, unless the lesion is inaccessible or the procedure is clinically contraindicated. In addition, a lymph node biopsy (excisional biopsy preferred over core needle biopsy or fine needle aspirate) and bone marrow aspirate are recommended with disease relapse or when disease progression is observed with 2 consecutive radiologic assessments, unless medically contraindicated. If possible, biopsy should be obtained from a nontarget lesion. The posttreatment biopsy and/or aspirate will be used for exploratory biomarker analyses including, but not limited to immunohistochemistry, targeted sequencing, and gene expressions analyses.

New Tumor Sample Biopsy for Second Primary Malignancy Assessment

If second primary malignancy is suspected, a fresh tumor biopsy may be collected for potential analysis of CAR transgene and insertional site analysis including CK and Pharmacodynamic Measurements

9.4.18.3 Blood Sample for DNA and Flow Cytometry (CK)

TAK-007 CK will be evaluated in blood and bone marrow samples by a validated polymerase chain reaction (PCR) method. For all patients treated with TAK-007, the CK profile and parameters, including but not limited to C_{max}, t_{max}, t_{last}, and AUC_{last}, will be reported. In addition, the number of TAK-007–expressing cells in the blood may be tracked by flow cytometry as an exploratory endpoint. The assessment of TAK-007 CK will be used to examine the exposure-response relationship, as well as the possible correlation of persistence and expansion of TAK-007 with safety and efficacy endpoints. Peripheral blood for CK will be collected as indicated in Appendix A,Table A 2.and Table A 3. In addition, bone marrow samples for assessment of CK will be obtained at all time points where bone marrow biopsy/aspirate is prescribed in the SOE (Appendix A, Table A 1). Details of the sample collection procedures for these assays are provided in the laboratory manual.

The timing may be adjusted and the total number of samples may be reduced during the study on the basis of emerging CK data. Additional confirmatory testing may be performed for patients with detectable transgene during long term follow-up.

9.4.18.4 Plasma Sample for Pharmacodynamics: Cytokines

Plasma samples will be collected to monitor the TAK-007–induced changes in cytokines, including IL-15. Additional soluble factor analyses may be conducted with emerging data. Sample collections for plasma cytokines, and inflammatory and safety biomarkers are mandated during the first 28 days following TAK-007 administration. However, the time-course and rapidity of CRS development and other toxicities, such as TLS, varies among patients. Additional unscheduled samples to better inform these individual differences may also be collected as needed, if it is clinically feasible. Any unscheduled inflammatory markers or

laboratory results will be recorded. In addition to cytokines defined in the protocol, an exploratory analyses of plasma using multiplexed proteomic approaches may be conducted.

9.4.18.5 Blood Samples for T/B/NK Absolute Counts and B-cell Aplasia

Blood samples will be collected for absolute quantification and frequency determination of lymphocytes (T cells, B cells, and NK cells) during the primary follow-up phase of the study.

9.4.19 Biomarker and Pharmacodynamic Measurements

In this study, several biomarker measurements will be assessed to test for correlations with safety and efficacy. These biomarkers will be used to identify potential pharmacodynamic activity in patients who have a greater likelihood of response or adverse reactions. The biomarker and pharmacodynamic specimen collection time points are displayed in Appendix A,Table A 2. Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

9.4.19.1 Blood Sample for HLA and KIR Typing

A blood sample will be collected to extract DNA for sequencing, the analyses will include, but may not be limited to, KIR genotyping and HLA typing.

9.4.19.2 Blood Samples for RCR

Blood samples will be collected to examine RCR during the course of the study. RCR testing will be done at pretreatment and at 3, 6, and 12 months for the first year after TAK-007 administration or until 2 consecutive negative results, whichever comes later. If all post-treatment assays for an individual patient are negative during the first year, collection of the yearly follow-up samples may be discontinued for that individual (Appendix A, Table A 2 and Table A 3).

If a positive RCR assay result is obtained from a blood specimen, the investigator will be informed, and the patient will be scheduled for an RCR retest. All positive RCR tests must be submitted as an SAE within the timeline described in Section 10.2 of the protocol. If deemed necessary, a more extensive patient monitoring plan will be developed in consultation with health authorities such as the US Food and Drug Administration (FDA).

9.4.19.3 Blood Samples for Immunophenotyping

Blood samples will be collected for assessment of CAR-NK phenotype and host immunophenotypic changes induced by TAK-007. 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 RNAseq.

9.4.19.4 Plasma Samples for ctDNA

Plasma samples from peripheral blood will be collected for assessment of tumor burden and genetic profiles using ctDNA over the course of the study. In addition to plasma, buffy coat cells will be collected for isolating cellular DNA to filter out germline variants.

9.4.19.5 Immunogenicity Sample Collection

Serum samples for the assessment of humoral immunogenicity and blood samples for the assessment of cellular immunogenicity will be collected. Samples must be collected before lymphodepleting chemotherapy, and as specified in the SOE (Appendix A, Table A 1 and Table A 3) 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 will also be collected if IRR/hypersensitivity is observed.

9.4.20 Sample Retention

Tumor tissue and bone marrow samples, peripheral blood mononuclear cells (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, 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 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, except in the case of positive RCR results for safety reporting purposes. Test results should not be discussed with a patient unless required by local law.

9.4.21 Sample Use for Research Purposes

The function of TAK-007 cells is not fully elucidated because CAR^+ NK cell therapy is an evolving field. Tumor tissue biopsy samples, PBMCs, and serum/plasma samples collected as part of the study under sample retention (Section 9.4.20) may be analyzed using new assays or platforms to test hypotheses relevant to disease biology, immuno-oncology, and cell therapy outside of TAK-007 clinical study. Research analyses may include, but are not limited to, cell functional assays, targeted DNA and RNA sequencing, immunohistochemistry, and/or flow cytometry.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they receive one dose of TAK-007.

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they have completed the 15-year LTFU phase, or if the patient has been withdrawn from the study (see Section 9.8).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

For patients who receive a single dose of TAK-007, discontinuation of treatment is applicable only to the conditioning phase of the study and during TAK-007 administration and not after TAK-007 was completely administered.

For patients who passed the screening phase but could not receive lymphodepleting therapy or TAK-007 (including incomplete administration), the reasons will be documented on the eCRF. Patients who passed the screening phase but could not receive lymphodepleting therapy or TAK-007 may be replaced in the study. Additional patients may be enrolled if deemed appropriate.

9.8 Withdrawal of Patients From Study

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

- Death.
- Lost to follow-up.
- Study terminated by sponsor.
- Consent withdrawal.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database. All data that has been collected to that point will remain in the database and can be subsequently used for analyses.

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, PFS, OS, and Safety)

Patients who complete study treatment will continue to have PFS and OS follow-up visits. The primary treatment follow-up visits should be conducted per the SOE listed in Appendix A, Table A 1 and Table A 2 for up to 6 months after TAK-007 administration.

Patients who experience PD or start a new systemic anticancer treatment will return for the subsequent visits with a smaller set of assessments. For example, a patient with documented disease progression at the Day28/Month 1 visit should still follow the assessments listed for the Day 28/Month 1 visit, will not return for the regular Month 2 and Month 4 visits, but will return

at Month 3 and Month 6 for assessments. Patients who receive subsequent new systemic anticancer therapy without documented disease progression should continue to undergo radiologic disease assessments as per Appendix A, Table A 1, until documented disease progression. Patients who have not yet experienced disease progression at the time of implementation of Protocol Amendment 5 will no longer have to undergo additional radiological disease assessments outside of standard of care.

The OS follow-up should be conducted according to Appendix A, Table A 1 and Table A 3, even outside the scheduled follow-up visits in the SOE, and also for patients with PD or who received new anticancer treatment. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, review of medical records at the site, 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 phase. See the SOE (Appendix A, Table A 1) 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.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or patient 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 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 G and Appendix H); 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 I to Appendix M). 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 1000/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.

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 (refer to 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.

SAEs must be reported (refer to 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 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).

RCR positivity is considered an SAE for this study and must be reported as such.

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 (TAK-007) or (2) conditioning (lymphodepleting) chemotherapy. The relationship is indicated by a yes or no response and entered into the eCRF.

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.

From signed informed consent through Month 6:

- For patients who receive TAK-007, including patients who experience disease progression and receive new anticancer systemic therapy, all AEs, both nonserious and serious, regardless of causality, will be continuously monitored and recorded.
- For patients who receive lymphodepleting chemotherapy and **do not** receive TAK-007, all AEs, both nonserious and serious, regardless of causality, will be collected for the first 30 days following lymphodepleting chemotherapy.

After Month 6 until EOS (ie, up to 15 years after TAK-007 administration), for all patients who receive TAK-007, including patients who experience disease progression and receive new anticancer systemic therapy, all AEs that meet the following criteria will be collected.

- All SAEs that are at least possibly related to TAK-007, lymphodepleting chemotherapy, or study procedures; these should be recorded on the appropriate page of the eCRF and reported to Takeda as directed in Section 10.2. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness.
- All events leading to death.
- All new incidences of Grade ≥3 infections, including opportunistic infections, that are at least possibly related to TAK-007 or lymphodepleting chemotherapy.
- All new incidences of Grade ≥3 hematologic disorders that are at least possibly related to TAK-007 or lymphodepleting chemotherapy.
- All new incidences OR Grade ≥3 exacerbations of prior neurological, rheumatological, or autoimmune disorders.
- Any new malignancy, other than the primary malignancy.
- Positive RCR results (always report as serious).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Patients and their partners 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 TAK-007 administration. If a patient or partner of a patient becomes pregnant or suspects that they are pregnant while participating in this study, they 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.

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).

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 the EMA, 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 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. Drugs will be coded using the 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.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 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.

13.0 STATISTICAL METHODS

13.1 General Considerations

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.

The primary analysis will be conducted and documented in a CSR after all dosed patients in the study have had the opportunity to be assessed for response and safety for at least 6 months after TAK-007 administration. Additional analyses may occur after the primary analyses have been completed. These additional analyses will be descriptive. The data cutoff for final analysis for the CSR addendum will be conducted after all dosed patients have had the opportunity to complete LTFU or if the study has been terminated by the sponsor.

All the endpoints (by dose levels in dose escalation, and by disease cohorts and dose regimens in expansion cohorts) will be summarized separately, unless specified otherwise.

13.2 Determination of Sample Size

Approximately 42 patients at dose levels of either 200×10^6 (±30%) or 800×10^6 (±25%) CD19 CAR^+ viable NK cells per patient will be enrolled.

13.3 Analysis Sets

The analysis sets will include the following:

- ***ITT set:*** All enrolled patients in the TAK-007 study. This set will primarily be used for disposition of patients.
- ***Safety analysis and modified intent-to-treat (mITT) sets:*** Patients who have received TAK-007 administration. This set will be used for safety analyses (safety set), and efficacy analysis to inform RP2D.
- ***Response-evaluable analysis set:*** Patients who have received TAK-007 administration, have had measurable disease at baseline, and at least 1 posttreatment radiologic assessment of disease response. This set will primarily be used for sensitivity analyses of efficacy endpoints, ORR and CR.
- ***CK analysis set:*** Patients receiving treatment with TAK-007 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.
- ***Per-protocol (PP) set:*** The PP set will include all enrolled patients who do not have a major protocol violation. All decisions to exclude patients from the PP set will be made before the database lock.

13.4 Analysis of Demographics and Other Baseline Characteristics

Patient disposition, demographic, and baseline characteristics will be summarized descriptively based on the ITT set and the mITT set. 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 Analyses

The mITT set will be used to inform the RP2D decision. The analyses of primary and secondary endpoints will be summarized by dose levels in dose escalation cohorts, and by disease cohorts and dose regimens in expansion cohorts.

In the event a patient undergoes an SCT or any other systemic anticancer therapy while on study, the patient's best response will be derived only based on evaluation before SCT or initiation of a new therapy, whichever occurs earlier. All patients who do not meet the criteria for an objective response by the analysis cutoff date will be considered nonresponders within the response-related analyses.

13.5.1 Efficacy Analysis of the Primary Endpoint

No longer applicable to the study as of Protocol Amendment 5.

13.5.2 Efficacy Analyses of the Secondary Endpoints

The analysis of the secondary efficacy endpoints includes ORR by investigator, CR by investigator, DOR by investigator, PFS by investigator, and OS.

ORR and CR and the corresponding exact 2-sided 95% CIs will be provided.

The time-to-event endpoints will include the following:

- DOR is defined only for patients who experience an objective response and is the time from the date of first documented objective response to the date of first documented disease progression per Lugano classification (Appendix D) or death, whichever comes first. Patients not meeting the criteria for progression or death will be censored at the last disease assessment.
- PFS in the ITT set is defined as the time from enrollment date to the date of disease progression per Lugano classification (Appendix D) or death from any cause, whichever comes first. PFS in the mITT set is defined as the time from TAK-007 administration to the date of disease progression or death from any cause, whichever comes first. Patients who do not have disease progression or die will be censored at the last disease assessment.
- OS in the ITT set is defined as the time from enrollment to the date of death from any cause. OS in the mITT set is defined as the time from TAK-007 administration to the date of death. Patients who do not die will be censored at the last contact date.

For time-to-event endpoints, including DOR, PFS, and OS, Kaplan-Meier plots, estimates and median values (if estimable) along with their 2-sided 95% CIs, will be computed. Estimates of the proportion of patients event-free at 3-month intervals will be provided. The censoring rules will be detailed in the SAP.

For the primary and secondary efficacy endpoints, subgroup analyses will be performed by disease subtypes, prespecified baseline, or other potential prognostic factors, which will be detailed in the SAP.

Further details of the analyses of the primary and secondary efficacy endpoints, including sensitivity analyses, will be prespecified in the SAP.

13.6 Safety Analysis

The safety set will be used for all safety analyses. 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 EOS.

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 G and Appendix H), 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 I to Appendix M). 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 levels using the safety set.

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.

13.7 CK Analysis

CK-related parameters will be estimated using noncompartmental methods. As permitted by data, CK parameters (eg, C_{max}, t_{max}, t_{last}, AUC_{last}) will be estimated from the TAK-007 concentration time profiles using the CK analysis set. CK parameters will be summarized using descriptive statistics, as permitted by data by dose level and indication.

Individual TAK-007 concentration-time data and individual CK parameters may be presented in listings and also tabulated using summary statistics by dose cohort and indication. Individual and mean concentration-time profiles will be plotted by dose cohort.

13.8 Pharmacodynamic Analysis

Frequency and percentage of patients with B-cell aplasia will be summarized before and after TAK-007 administration by scheduled time point using the pharmacodynamic analysis set.

Concentration of soluble immune factors in circulation (eg, IL-15, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, tumor necrosis factor alpha, granulocyte macrophage colony-stimulating factor) in plasma will be tabulated using summary statistics over scheduled time point. Individual and mean concentration-time profiles may also be plotted.

13.9 Immunogenicity Analyses

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

13.10 RCR Analyses

Frequency and percentage of patients with positive RCR test results will be summarized by scheduled time point before and after TAK-007 administration using safety analysis set.

13.11 Exploratory Analyses

13.11.1 Population CK-Pharmacodynamic Analysis

The relationship between TAK-007 systemic exposure and safety, efficacy, and pharmacodynamic response (eg, B cell aplasia, time to B cell recovery, changes in cytokines/chemokines) will be evaluated to understand the CK-pharmacodynamic relationship of TAK-007. The results from this PK/PD analysis will be presented in a separate report.

13.11.2 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.

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.

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 IEC, 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 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). 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 (ie, 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 B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

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.

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.

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, Japan Pharmaceuticals and Medical Devices Agency of Japan), 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 (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 general packaging 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.

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 clinicaltrialsregister.eu, 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

Table A 1 Schedule of Events for All Patients up to Month 6

Phase	Screening Phase [a]	Conditioning Phase LDC	Treatment and Primary Follow-up Phase											
Days	≤28 days Before LDC	D -5, -4, -3	D0 [b]	D1	D3	D7	D10	D14	D21	D28/ M1	M2	M3	M4	M6
Visit window				±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d	±14 d	±14 d	±14 d
Informed consent	X													
Inclusion/exclusion criteria	X													
Medical history and patient demographics	X													
ECHO or MUGA	X													
ECOG performance status	X	Day -5 (before LDC)								X	X[c]	X[c]	X[c]	X[c]
12-lead ECG	X	Day -5 (before LDC)												X[c]
Pregnancy tests [d]	X	Day -5 (before LDC)	As clinically indicated											
Height and weight [e]	X	Day -5 (before LDC)								X	X[c]	X		X
Safety assessments														
Physical examination	X	Day -5 (before LDC)	X	X	X	X	X	X	X	X	X[c]	X	X[c]	X
Vital signs and SpO_2	X	D -5 to D -3	X [f]	X	X	X	X	X	X	X	X[c]	X	X[c]	X
Hematology, serum chemistry, coagulation, serum immunoglobulins [g]	X	Day -5 (before LDC)	X [h]	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]

Table A 1 Schedule of Events for All Patients up to Month 6

Phase	Screening Phase [a]	Conditioning Phase LDC	Treatment and Primary Follow-up Phase											
Days	≤28 days Before LDC	D -5, -4, -3	D0 [b]	D1	D3	D7	D10	D14	D21	D28/ M1	M2	M3	M4	M6
Visit window				±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d	±14 d	±14 d	±14 d
Safety assessments (continued)														
Virus tests (CMV, HBV, HCV, HIV)	X	For patients with evidence of prior exposure to HBV or HCV: HBV DNA or HCV RNA at D28/M1, M2, M3, M4, and M6. For all other cases: Test as clinically indicated OR if ALT > 3 × ULN. Patients who are HIV-positive but have a negative viral load at screening must continue to have HIV viral load monitored per institutional guidelines for the duration of the study. Not required for a patients with documented disease progression and/or begins a new systemic anticancer treatment at the prior visit.												
Concomitant medications and procedures	<---------- X ---------->													
AE [i]	<---------- X ---------->													
Survival follow-up [j]												X		X
Study Intervention														
LDC		D -5, -4, -3												
TAK-007 Administration			X [b]											
Disease assessments														
Lymphoma tissue collection	X					(Range of D7-D14)								
Disease assessment per Lugano classification [l]	X									X		X[c]		X[c]
BM biopsy [m]	X									Mandatory for iNHL at the time of CR in imaging (for patients with previous BM involvement)				
BM aspirate [n]	X					(Range of D7-D14)				Recommended for iNHL at the time of CR in imaging (for patients with previous BM involvement) and recommended at relapse (for all patients)				

Table A 1 Schedule of Events for All Patients up to Month 6

Phase	Screening Phase [a]	Conditioning Phase LDC	Treatment and Primary Follow-up Phase											
Days	≤28 days Before LDC	D -5, -4, -3	D0 [b]	D1	D3	D7	D10	D14	D21	D28/ M1	M2	M3	M4	M6
Visit window				±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d	±14 d	±14 d	±14 d

AE: adverse event; ALT: alanine aminotransferase; BM: bone marrow; CMV: cytomegalovirus; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; FFPE: formalin-fixed paraffin embedded; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; iNHL: indolent non-Hodgkin lymphoma; IWG: International Working Group; LBCL: large B-cell lymphoma; LDC: lymphodepleting chemotherapy; M: month; MUGA: multigated acquisition scan; PD: progressive disease; PET: positron emission tomography; RNA: ribonucleic acid; 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 events 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 0 will be defined as the actual day of first TAK-007 administration, hence the reference of all subsequent dates.

After the Day 28 visit, each month will count as 30 days.

[a] The screening visit must occur within 28 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] Not required for a patient with documented disease progression and/or begins a new systemic, anticancer therapy at the prior visit.

[d] 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.

[e] Height to be measured at screening only.

[f] Vital signs and SpO_2: Before TAK-007 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 TAK-007 administration.

[g] Coagulation will only be assessed at screening and as clinically indicated. Immunoglobulins will not be assessed between Day 0 and Day 21.

[h] Hematology samples will be collected before TAK-007 administration and 1 hour (±15 minutes) after start of TAK-007 administration.

[i] Details on monitoring of AEs and period of observation during the primary follow-up phase are summarized in Section 10.3.

[j] Survival will be followed up for patients who receive TAK-007 administration. Survival will be followed-up every 3 months. 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).

[k] A lymphoma biopsy at screening is mandatory unless archived tumor lymphoma tissue (at least 10 unstained FFPE slides) collected after the last therapy is available. Sponsor waiver may be given on a case by case basis. For all patients, Days 7 to 14 biopsies will be optional. Biopsies at relapse are recommended. There should be no clinical contraindication and lymphoma should be easily accessible.

Table A 1 Schedule of Events for All Patients up to Month 6

Phase	Screening Phase [a]	Conditioning Phase LDC	Treatment and Primary Follow-up Phase											
Days	≤28 days Before LDC	D -5, -4, -3	D0 [b]	D1	D3	D7	D10	D14	D21	D28/ M1	M2	M3	M4	M6
Visit window				±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d	±14 d	±14 d	±14 d

[l] Disease assessment per IWG 2014 guidelines will be performed until PD by imaging, or additional lymphoma therapy except consolidating autologous or allogeneic stem cell transplantation. Assessments will be performed per local guidance.
[m] Baseline BM evaluation is required for all patients at screening except for patients with LBCL with confirmed BM involvement in PET-CT. Archived BM biopsy sample (and assessment) within 42 days before start of lymphodepleting chemotherapy is acceptable if no antitumor therapy was given after BM evaluation. After baseline evaluation, BM will be evaluated in patients with iNHL who had initial BM involvement and in whom, treatment achieved CR in imaging. There should be no clinical contraindication for BM evaluation.
[n] Optional BM aspiration for pharmacokinetics will be performed between Days 7 and 14. Based on the emerging data, collection from additional patients may be waived or made optional. BM aspirate is also recommended at relapse. There should be no clinical contraindication for BM evaluation.

Table A 2 Schedule of Events for All Patients up to Month 6 (Treatment and Primary Follow-up Phase) – Biomarker Sampling

Procedure	Conditioning Phase	Treatment and Primary Follow-up Phase								
	LDC	TAK-007 Administration	Post-treatment Follow-up							
	D -5 (before LDC Administration)	D0	D1	D3	D7	D10	D14	D21	D28/ M1	M2, M3, M4 and M6 [a]
Visit window	-4d		±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d (M2 only)/ ±14 d
Blood for DNA (CK)		X[b]	X	X	X	X	X	X	X	X
Blood for flow cytometry (CK)	X	X[b]		X	X	X	X	X	X	M2 and M6[c]
Blood (HLA and KIR typing)	X									
Blood for DNA (RCR)	X									M3 and M6
Blood for T/B/NK cells absolute counts	X	X (before TAK-007 administration			X				X	M2, M3 and M6[c]
Blood for immunophenotyping	X				X		X		X	M3 and M6[c]
Plasma for IL-15 and cytokine panel [d]	X	X (before TAK-007 administration)	X		X		X	X	X	M2 and M6[c]
Serum for humoral immunogenicity (anti-HLA and anti-CAR antibody)	X								X	X[c]
Plasma for ctDNA	X	X (before TAK-007 administration)					X		X	M3 and M6[c]
Blood for cellular immunogenicity	X								X	X[c]

Table A 2 Schedule of Events for All Patients up to Month 6 (Treatment and Primary Follow-up Phase) – Biomarker Sampling

Procedure	Conditioning Phase	Treatment and Primary Follow-up Phase								
	LDC	TAK-007 Administration	Post-treatment Follow-up							
	D -5 (before LDC Administration)	D0	D1	D3	D7	D10	D14	D21	D28/ M1	M2, M3, M4 and M6 [a]
Visit window	-4d		±1 d	±1 d	±1 d	±1 d	±2 d	±2 d	±4 d	±4 d (M2 only)/ ±14 d

CAR: chimeric antigen receptor; CK: cellular kinetics; ctDNA: circulating tumor DNA; D: day; HLA: human leukocyte antigens; IL 15 interleukin-15; KIR: killer immunoglobulin-like receptor; LDC: lymphodepleting chemotherapy; M: month; NK: natural killer; RCR: replication competent retrovirus.
Unless otherwise noted, evaluations during the conditioning and treatment phases must occur before LDC administration or TAK-007 administration. Tests and procedures should be performed on schedule for all visits. If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.
After the Day 28 visit, each month will count as 30 days.
[a] For patients who have documented progression at a prior visit and/or begin a new systemic anticancer treatment at a prior visit, only M3 and M6 samples are required where indicated.
[b] Samples will be collected before and after (1 hour ±15 minutes) TAK-007 administration.
[c] Sample is not required if patient has documented progression and/or begin a new systemic anticancer treatment at a prior visit.
[d] Additional samples may be collected during safety assessment if patient develops Grade 3 toxicity.

Table A 3 Schedule of Events for All Patients from Month 6 onwards

Procedure	Secondary Follow-up M12, M18, and M24 ±2 months	Long Term Follow-up Annually after M24 until 15 years ±3 months
Adverse events [a,b]	<---------- X ---------->	
Second primary malignancy evaluation	X	X
Survival follow-up [c]	X	X
New anticancer therapy	X	X[d]
Blood for DNA (CK) [e]	X	X
Blood for DNA (RCR)	M12 and M24[f]	X[f]
Serum for humoral immunogenicity (anti HLA and anti-CAR antibody)	M12	
Pregnancy test	As clinically indicated until M12	

AE: adverse event; CAR: chimeric antigen receptor; CK: cellular kinetic(s); D: Day; M: Month; PD: progressive disease; RCR: replication competent retrovirus; SAE: serious adverse event; SCT: stem cell transplantation.
Tests and procedures should be performed within the specified windows for all visits. If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor. 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.
Each month will count as 30 days.
[a] During secondary follow-up, all AEs with onset date more than 6 months until 24 months after TAK-007 administration should be reported according to criteria listed in Section 10.3.
[b] During LTFU, all related SAEs, all deaths, and new incidences of Grade ≥3 AEs that are at least possibly related to TAK-007 and/or lymphodepletion and relevant to the potential risks of TAK-007 will be collected (see Section 10.3).
[c] Survival follow-up should be conducted every 6 months in secondary and at least annually during the long-term follow-up phases. 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, medical records review, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).
[d] New anticancer therapy need not be collected if samples for CK (DNA) are no longer being taken after Month 24.

Table A 3 Schedule of Events for All Patients from Month 6 onwards

	Secondary Follow-up	Long Term Follow-up
	M12, M18, and M24	Annually after M24 until 15 years
Procedure	±2 months	±3 months

[e] If CAR transgene is detectable at Months 24, 36, or 48, additional samples will be collected within the next 6 months ie, at Months 30, 42, and 54, respectively, for further clonality assessment.
[f] If all post-treatment assays for an individual patient are negative during the first year, collection of the yearly follow-up samples may be discontinued for that individual.

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 Code of Federal Regulations (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.
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.

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.

Appendix D IWG 2014 (Lugano) Response Criteria for Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	*Complete metabolic response*	*Complete radiologic response (all the following)*
Lymph nodes and extralymphatic sites	Score 1, 2, or 3, with or without a residual mass on the 5-point scale [a]	Target nodes/nodal masses must regress to ≤1.5 cm in the longest transverse diameter of all lesions No extralymphatic sites of disease
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, immunohistochemistry negative
Partial	*Partial metabolic response*	*Partial remission (all the following)*
Lymph nodes and extralymphatic sites	Score of 4 or 5 [a] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in sum of the product of the perpendicular diameters of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	*No metabolic response*	*Stable disease*
Target nodes/nodal masses, extranodal lesions	Score 3, 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in sum of the product of the perpendicular diameters of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	*Progressive metabolic disease*	*Progressive disease requires at least 1 of the following*
Individual target nodes/nodal masses	Score 3, 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: Longest transverse diameter of a lesion >1.5 cm and Increase by ≥50% from nadir cross product of the longest transverse diameter and perpendicular diameter and An increase in longest transverse diameter of a lesion or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond nadir (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from nadir. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Source: Adapted from (Cheson et al. 2014).

[a] PET 5-point scale: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

CT: computed tomography; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; IWG: International Working Group; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the products of the perpendicular diameters for multiple lesions.

Appendix E 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).

Appendix F 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).

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 G 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.

Appendix H 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] 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.

Appendix I 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 J and Appendix K for acute and chronic GvHD features.

Appendix J 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.

Appendix K 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).

Appendix L 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):*_____				

Source: (Jagasia et al. 2015).

	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).

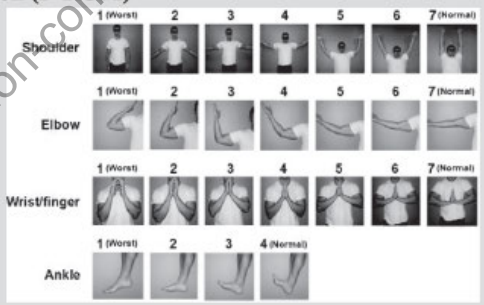
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **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)



Source: (Jagasia et al. 2015).

Appendix M 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).

Appendix N BOIN Design

The Bayesian optimal interval (BOIN) design (Liu and Yuan 2015), (Yuan et al. 2016), (Zhou et al. 2018) will be used to guide the dose escalation and the MTD estimation. This study was designed and will be conducted using the software BOIN that is available at trialdesign.org (trialdesign.org, Integrated Platform for Designing Clinical Trials, Accessed 21 June 2021).

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 12. Each time we will enroll and treat patients in a cohort size of approximately 3. 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 ≤ 0.197, 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 > 0.298, 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 12 is reached, or until the number of evaluable patients treated at the current dose reaches 6 and the decision according to above is to stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level $j, j = 1,\cdots, 2$. 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 (Section 6.1), which will be used to conduct the study.

After the dose escalation is complete, the MTD is selected based on isotonic regression as specified in Liu and Yuan (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 are evaluated with simulations assuming various distributions of toxicity across dose levels shown in Table T 1 below.

Table T 1: Simulation Scenarios

	True DLT Rate		
TAK-007 Dose Level	**Scenario 1**	**Scenario 2**	**Scenario 3**
200M	0.05	**0.25**	0.08
800M	0.15	0.43	**0.25**

The operating characteristics calculated from the simulations are shown in Table T 2 below.

Table T 2: Operating Characteristics

TAK-007 Dose Level	**Scenario 1**		**Scenario 2**		**Scenario 3**	
	Selection %	**% Patients Treated**	**Selection %**	**% Patients Treated**	**Selection %**	**% Patients Treated**
200M	9.6	44.6	**76.97**	67.8	29.27	50.7
800M	**90.4**	55.4	18.03	32.2	**70.70**	49.3
% Early Stopping	0		5		0.03	
Expected # of Patients	10.4		9.2		10.7	

Note: Out of 3,000 simulations, "% early stopping"" refers to the percentage of early stopping due to excessive DLT; "Selection %" refers to the percentage of selecting this dose as the MTD.

Appendix O 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
Grade 2	**Hypotension**	• Cardiac telemetry • Fever work-up if not previously performed o 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 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 o 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 o 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

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 o 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 o 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)
Grade 4	**Hypotension**	• Obtain ECHO if not performed already • Cardiac telemetry • Fever work-up if not previously performed o 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 o Assess for infection with blood and urine	• Transfer patient to ICU • Positive pressure ventilation including CPAP, BiPAP, mechanical ventilation • Symptomatic management of fever as in Grade 1 CRS • Supplemental oxygen including	• 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

CRS Grade	CRS Parameter	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
		cultures, and chest radiography	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	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)

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

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, leptomeningeal 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

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	**Supportive Care**	**Anti-IEC Therapies**
				tocilizumab[1]
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

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
Cyclophosphamide	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

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

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

Adapted from IEC Therapy Toxicity Assessment and Management (also known as CARTOX) -Adult V4

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, uremia, and/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, emboli, vasculitis, strokes, and/or seizure-related changes.

Appendix P Protocol History

Date	Amendment Number	Amendment Type	Region
03 June 2024	Amendment 5	Substantial	Global
20 December 2023	Amendment 4	Substantial	Global
29 April 2022	Amendment 3	Substantial	Global
21 December 2021	Amendment 2	Substantial	Global
12 July 2021	Amendment 1	Substantial	Global
05 May 2021	Initial protocol	Not applicable	Global

Protocol Amendment 4 Summary and Rationale

This section describes the changes to the protocol incorporating Amendment 4.

The primary reason for this amendment is to update the study design of Part 1 with two additional expansion cohorts to evaluate the administration of >1 dose of TAK-007, after a single cycle of lymphodepleting chemotherapy, including appropriate safety and tolerability risk mitigation. This amendment also opens enrollment to patients with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) who have failed one prior line of systemic anticancer therapy, removes the requirement for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing at screening, and clarifies monitoring of AEs and period of observation for all patients during posttreatment follow-up.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Figure 6.a Study Schematic for TAK-007-2001 Protocol Section 8.2 Prohibited Concomitant Medications and Procedures Section 9.4.3 Treatment and Follow-up Phases (Day 0 to Month 24) Appendix A, Schedule of Events Table A 1, Table A 2, Table A 3	The design of the expansion phase of Part 1 was updated to include 2 additional expansion cohorts for patients with r/r LBCL, evaluating the administration of >1 dose of TAK-007. In addition, r/r LBCL patients after 1 prior line of systemic anticancer therapy will be included. The administration of 3 weekly doses of TAK-007 after a single cycle of lymphodepletion is not expected to cause a clinically significant increase in toxicity; however, in addition to the robust TAK-007-2001 study safety management plan that is already in place, additional safety measures (14-day observation period and staggering between the first 2 patients; enrollment pausing criteria; and exclusionary safety criteria for patients who will not be eligible to receive their Day 7 and/or Day 14 dose of TAK-007) were added specifically for these 2 multi-dose expansion cohorts to mitigate any possible additional toxicity.	Based on the safety and tolerability profile of TAK-007 (no dose-limiting toxicities [DLTs], graft-versus-host disease [GvHD], or immune effector cell-associated neurotoxicity syndrome [ICANS] and very few events of low-grade cytokine release syndrome [CRS], the most common toxicities were hematological and related to lymphodepletion), the administration of up to 3 single doses of 800×10^6 CAR^+ NK cells (on Days 0, 7, and 14) following a single cycle of lymphodepletion may further enhance the clinical response rate without the additive risks associated with repeat lymphodepletion cycles.
2.	Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients Section 13.2 Determination of Sample Size	The number of patients in Part 1 of the study was increased for the planned patients in the multi-dose expansion cohorts.	Updated for revised study design
3.	Section 2.0 STUDY SUMMARY Section 6.3.4 Total Study Duration	Updated duration of enrollment to account for the increased observation time and staggered design of the multi-dose expansion cohorts of Part 1.	Updated for revised study design
4.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, #6	Added specifications on which patients with CD19-targeted therapies are eligible	Revised for clarification because of the evolving treatment landscape in LBCL with CD19-targeted therapies.

Protocol Amendment 4			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	Section 6.1 Overview of Study Design	Restricted enrollment of patients with prior CD19-targeting CAR-T cell therapy to ≤7 patients for Cohort 1B.	Updated for revised study design
6.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #6	Specified exclusionary time frame for rituximab treatment before initiation of conditioning therapy.	Revised for clarification
7.	Section 2.0 STUDY SUMMARY Section 8.1 Study Drug Administration Section 9.3 Treatment Group Assignments Section 9.4.3 Treatment and Follow-up Phases (Day 0 to Month 24) Appendix A, Schedule of Events Table A 1	Study drug administration details were updated for the multi-dose expansion cohorts, including a delay for up to 7 days each before the second and third TAK-007 dose to allow for recovery from AEs and the addition of exclusionary safety criteria for patients who will not be eligible to receive their second and/or third dose of TAK-007, including possible dose reduction for subsequent TAK-007 dose administration in patients with Grade ≥3 cardiac or pulmonary toxicity at least possibly related to TAK-007, after resolution to baseline.	Updated for revised study design
8.	Section 2.0 STUDY SUMMARY Section 9.4.13 AEs Section 9.10 Posttreatment Follow-up Assessments (DOR, PFS, OS, and Safety) Section 10.3 Monitoring of AEs and Period of Observation Appendix A, Schedule of Events Table A 1, Table A 3.	The monitoring of AEs and period of observation for all patients during posttreatment follow-up was adapted to detail the proper safety follow up phase for patients with disease progression with or without new systemic anticancer therapy, and for patients who received lymphodepletion therapy, but did not receive TAK-007. In addition, the types of AEs and the period of collection was limited to reduce excessive reporting and unnecessary AE collection.	Revised for clarification. Also refined and clarified AE collection to reduce excessive reporting and for better characterization of the expected short-term and long-term risks of TAK-007.

Protocol Amendment 4			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9.	Section 2.0 STUDY SUMMARY Section 13.1 General Considerations Section 13.5 Efficacy Analyses	Added specifications for summarizing endpoints in Part 1 (dose escalation and dose expansion phase) and the primary analysis assessment of Part 2 by an independent review committee.	Updated for revised study design and clarification.
10.	Section 4.1.5 Clinical Experience	Updated information and added current status of the study.	Clarification
11.	Section 6.3.1 Duration of an Individual Patient's Study Participation	Revised to include the multi-dose cohorts in the dose expansion phase of Part 1.	Updated for revised study design
12.	Section 8.5 Management and Mitigation of AEs Associated With CAR Cell Therapy Table 8.a CAR-T Toxicity Assessment and Management Guidelines	Revised to include monitoring, assessment, and management guidelines for handling TAK-007 product batches in the multi-dose expansion cohorts, after the occurrence of a Grade ≥2 acute GvHD AE. Revised monitoring, assessment, and management guidelines for tumor lysis syndrome.	Updated for revised study design and clarification.
13.	Section 8.6 Definition of DLTs	Specified that DLTs occur only in the Dose Escalation phase of Part 1	Revised for clarification
14.	Section 8.7 Enrollment Pausing Criteria	Revised enrollment pausing criteria to include pausing during the dose escalation phase and the dose expansion phase (for multi-dose cohorts) of Part 1	Updated for revised study design
15.	Section 9.4.1 Screening Phase (Day -33 to Day -6) Section 9.4.16 Clinical Laboratory Evaluations	Removed requirement for SARS-CoV-2 testing from infectious disease test at screening.	Updated due to endemicity of COVID-19.
16.	Section 9.4.16 Clinical Laboratory Evaluations Appendix A, Schedule of Events Table A 1	Added requirements for HIV-positive patients with negative viral load at screening	Revised for clarification.

Protocol Amendment 4			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
17.	Section 9.4.18.1 Primary Specimen Collection Table 9.b Primary Specimen Collection Table 9.c Prioritized Sequence for Specimen Collection	The priority of plasma sample for ctDNA was changed to number 8 in Table 9.b, and to number 6 in Table 9.c.	Revised to increase probability of sample collection.
18.	Section 9.4.18.2 Tumor and Bone Marrow Biopsies and Aspirates Appendix A, Schedule of Events Table A 1	Removed mandatory bone marrow aspiration at Month 3.	Revised to reduce patient burden.
19.	Section 9.4.21 Healthcare Resource Utilization	Added clarification that healthcare resource utilization will only be evaluated in Part 2 of this study.	Revised for clarification.
20.	Section 9.5 Completion of Study Treatment (for Individual Patients) Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Updated to include definitions for the added cohorts with multi-dose regimen of TAK-007.	Updated for revised study design

Protocol Amendment 3 Summary and Rationale

This section describes the changes to the protocol incorporating Amendment 3.

The primary reason for this amendment is to modify several exclusion criteria to broaden the enrollment of eligible patients into the study. This amendment also removes all Day 5 laboratory evaluations as Day 5 will likely take place on a weekend day, which is logistically impractical for this study. Imaging requirements have also been updated to reduce patient exposure to positron emission tomography (PET) scans beyond 6 months posttreatment.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 3			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Appendix A, Schedule of Events Tables 1 and 2	Removed all Day 5 laboratory evaluations and research sampling.	Revised because of the increased likelihood of the Day 5 visit occurring on a weekend; this visit is removed for site resourcing and laboratory practicality reasons.
2.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #2	Reworded this exclusion criterion to clarify that patients with a history of secondary involvement by lymphoma without evidence of central nervous system (CNS) involvement at screening can be enrolled.	Revised for clarity.
3.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #3	Created a separate exclusion criterion for patients with Burkitt lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, or transformation from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (Richter transformation).	Revised for clarity.
4.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria #3 (Amendment 2 numbering)	Removed the criterion excluding patients with a history of anti-CD19 therapy (eg, CD19-targeted chimeric antigen receptor [CAR] T cells or monoclonal antibodies).	Revised because of the evolving treatment landscape in large B-cell lymphoma (LBCL) with CD19 targeted therapies moving into the second line setting. Additionally, natural killer (NK) cells are hypothesized to kill tumor cells upon target antigen downregulation via innate immune receptor-mediated killing.
5.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #5	Added to this criterion the exclusion of patients who have undergone chimeric antigen receptor T-cell (CAR-T) therapy within 3 months of planned enrollment.	Revised to allow sufficient time for patients to recover after CAR-T therapy.

Protocol Amendment 3			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #6	Reworded this criterion to (1) exclude patients who receive any systemic anticancer treatment within 14 days before conditioning therapy and (2) revise the 14-day time frame to include 2 half-lives of the treatment (whichever is longer) before conditioning therapy.	Revised to allow adequate washout periods for patients who may have received prior systemic anticancer treatments. In addition, included a half-life–based washout period for agents with long half-lives.
7.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #7	Reworded this criterion for emphasis on active fungal, bacterial, and viral infections.	Revised for clarity and to remove redundancy.
8.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #8	Removed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from this criterion.	Revised to eliminate redundancy with exclusion criterion #7.
9.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #9	Reworded this criterion to exclude patients with active or clinically relevant CNS disorders and severe dementia. Reworded this criterion to permit enrollment of patients without recurrence of a CNS disorder within 2 years of planned study enrollment.	Revised for clarity. Revised as limited risk of CNS events expected with CAR-NK cell therapy.
10.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #10	Reduced the time frame from 12 months within enrollment to 6 months within enrollment for patients with specified exclusionary cardiac events.	Revised as a limited risk of cardiac events is expected with CAR-NK cell therapy.
11.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, #12 (Amendment 2 numbering)	Removed exclusion criterion #12.	Revised as a limited risk of thromboembolic events is expected with CAR-NK cell therapy.
12.	Section 5.2.3 Exploratory Endpoints	Added tumor volume on computed tomography (CT)/magnetic resonance imaging (MRI) and volumetric tumor assessment.	Revised to provide additional details on endpoints that will be assessed.
13.	Section 9.4.1 Screening Phase (Day -33 50 Day -6) Section 9.4.16 Disease Assessments	Removed wording that excludes marginal zone lymphoma (MZL) from positron emission tomography (PET) imaging.	Revised as MZL may have fluorodeoxyglucose (FDG) avidity.

Protocol Amendment 3			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	Section 9.4.2 Conditioning Phase (Day -5 to Day -1)	Added wording that patients with symptomatic SARS-CoV2 infection must not initiate lymphodepleting chemotherapy.	Revised for clarity.
15.	Section 9.4.2 Conditioning Phase (Day -5 to Day -1) Section 9.4.15 Clinical Laboratory Evaluations	Replaced creatinine clearance with estimated glomerular filtration rate (GFR) in the "NOTE" defining lymphodepleting chemotherapy administration in Section 9.4.2 and in text in Section 9.4.15.	Revised for accuracy.
16.	Section 9.4.16 Disease Assessments	Removed mention of response assessment by independent central review as it is not being done in Part 1 of this study. Updated text to reduce exposure to PET scans beyond 6 months posttreatment. Added recommendation to avoid scheduling imaging scans and SARS-CoV-2 vaccination or booster within 2 weeks of each other.	Revised for clarity regarding timing of imaging for disease assessment and what scans to perform. Revised to reduce exposure to PET imaging for patients who do not have FDG-avid disease. Added recommendation to avoid possible confounding observations on imaging scans, as SARS-CoV-2 vaccination has been shown to cause transient lymphadenopathy that may make mimic that of lymphoma.
17.	Section 9.4.17.1 Primary Specimen Collection	Added language that blood samples should be drawn before dosing on days when lymphodepleting chemotherapy is administered.	Revised for clarity.
18.	Appendix A, Schedule of Events Tables 1	Reduced vital signs and oxygen saturation (SpO_2) assessments from daily to Day (D)1, D2, D3, and D7.	Revised as a limited risk of acute toxicity by CAR-NK treatment is expected and to reduce patient burden.
19.	Appendix A, Schedule of Events Tables 2	Removed Month (M)36 and M48 circulating tumor DNA (ctDNA) sample collection.	Revised to reduce sampling.
20.	Appendix A, Schedule of Events Tables 2, Footnote d	Added new footnote for additional ctDNA sample to be drawn at time of documented progression of disease.	Revised for clarity.

Protocol Amendment 3			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
21.	Appendix J IWG 2014 (Lugano) Response Criteria for Lymphoma	Replaced baseline with nadir and added PET 5-point scale.	Revised for accuracy and clarity.

Protocol Amendment 2 Summary and Rationale:

This section describes the changes to the protocol incorporating Amendment 2.

The primary reason for this amendment is to provide additional guidance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing and management in cellular therapy patients.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purpose only.

Protocol Amendment 2			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 8.3 Permitted Concomitant Medications and Procedures	Added premedications to permitted medications and procedures.	Revised for clarity.
2.	Section 9.4.1 Screening Phase (Day -33 to Day -6) Section 9.4.15 Clinical Laboratory Evaluations Appendix A Schedule of Events (SOE)	Extended polymerase chain reaction (PCR) test window for SARS-CoV-2 from within 7 days to within 10 days of lymphodepleting chemotherapy initiation and included guidance for SARS-CoV-2 testing prior to cellular therapy.	Revised to allow better planning of treatment schedules and included guidance for SARS-CoV-2 testing prior to cellular therapy.
3.	Section 10.3 Monitoring of AEs and Period of Observation	Revised adverse event (AE) collection language to specify that, for patients who receive lymphodepletion chemotherapy but do not go on to receive TAK-007, all AEs will be collected for the first 30 days following lymphodepleting chenotherapy and that after that, only treatment-related AEs would be collected.	Revised for clarity.

Protocol Amendment 2			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 14.1 Study-Site Monitoring Visits	Added statement regarding remote site monitoring.	Revised to allow improved site monitoring.
5.	Appendix A Schedule of Events Tables 1, 2, and 3	Deleted statement in table notes regarding visit windows.	Revised for clarity.

Protocol Amendment 1 Summary and Rationale:

This section describes the changes to the protocol incorporating Amendment 1.

The primary reason for this amendment was to address the changes requested by United States (US) Food and Drug Administration (FDA) during the Investigational New Drug (IND) application 27322 review.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purpose only.

Protocol Amendment 1			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Throughout protocol	TAK-007 dose of 800×10^6 (±30%) was revised to 800×10^6 (±25%)	Changes made in response to Food and Drug Administration's (FDA's) request for a tighter dose range.
		Removed "safety run-in" from Part 1 references as Part 1 includes assessments other than safety assessments.	Changes made for accuracy.

Protocol Amendment 1			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 9.3 Treatment Group Assignments	Part 1 of study is redesigned to be a sequential dose escalation guided by Bayesian Optimal Interval (BOIN) design followed by expansion cohorts to select the recommended phase 2 dose (RP2D). Separate expansion cohorts for large B-cell lymphoma and indolent non-Hodgkin lymphoma with approximately 15 patients each may be initiated for dose level(s) selected based on the dose escalation part, to further evaluate the safety, tolerability, efficacy and cellular kinetics and to allow the selection of the RP2D to be used in the rest of the study.	Changes made in response to FDA's request for a sequential, dose escalation study design.
3.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Part 1 of the study, the 7-day interval between the first and second patient in each dose level has been increased to a 21-day interval, and a new 28-day interval has been added between the 2 dose cohorts in Part 1 to allow for dose-limiting toxicity (DLT) assessment.	Changes made in response to FDA's request for additional time between the first 2 patients dosed and between dose cohorts to allow for safety monitoring and DLT assessment.
4.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Revised inclusion criterion # 6.e and deleted #6.f to indicate that single agent anti-CD20 mAb therapy is not considered a line of therapy for all patients (ie, both LBCL and iNHL).	Changes made per FDA recommendation.
5.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 8.4 Precautions and Restrictions	All references to the use of institutional guidelines have been removed from the protocol and only CAR-T cell therapy-associated TOXicity (CARTOX) guidelines will be used for the management of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).	Changes made to simplify and standardize CRS and ICANS management.
6.	Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients Section 13.2 Determination of Sample Size	Number of patients in Part 1 has been revised to reflect BOIN dose escalation design followed by expansion cohorts.	Changes made in response to FDA's request for sequential, dose escalation design.

Protocol Amendment 1			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7.	Section 2.0 STUDY SUMMARY	Study enrollment period was revised to match the study enrollment period in Section 6.3.	Change was made to correct prior error in the Study Summary.
8.	Section 2.0 STUDY SUMMARY Section 13.2 Determination of Sample Size	Sample size was revised to reflect the dose escalation design followed by expansion cohorts.	Changes made per FDA recommendation.
9.	Section 8.6 Definition of DLTs	DLT definition revised to clarify and include nonhematologic treatment-emergent adverse events (TEAEs) Grade ≥3 clearly unrelated to the underlying disease and at least possibly related to the investigational therapy (TAK-007 and/or lymphodepletion). Added acute graft-versus-host disease (GvHD) Grade 2 requiring systemic steroids and not resolving within 7 days to definition of DLTs.	Change made in response to FDA's request for inclusion of TEAEs at least possibly related to TAK-007 and/or lymphodepletion. Change made in response to FDA's request for inclusion of Grade 2 acute GvHD not resolving within 7 days to definition of DLTs.
10.	Section 8.7 Enrollment Pausing Criteria	Revised enrollment pausing criteria.	Changes made in response to FDA's request for clarification and revision of enrollment pausing criteria.
11.	Section 13.3 Analysis Sets	Added per-protocol set	Change made to clarify that per-protocol set would be used for additional supportive analysis of overall response rate (ORR) in Part 2 of the study.
12.	Section 13.5 Efficacy Analyses	Added statement regarding ORR analysis in Part 2 of study.	Change made to clarify that ORR in Part 2 will be analyzed in the per-protocol set as supportive analysis.
13.	Section 13.6 Safety Analysis	Deleted "TEAEs leading to study discontinuation" bullet from tabulated AEs categories. Added sentence to reflect the DLT assessment during the dose escalation.	Change made as this does not apply to this study. Changes made per FDA recommendation.

Protocol Amendment 1			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	Section 13.12 Statistical Considerations for Dose Selection at the End of Part 1	Deleted this section.	Change made as it no longer applies to the new study design to address the comments by the FDA.
15.	Appendix T BOIN Design	Added BOIN Design appendix to provide further details regarding BOIN study design.	Change made as part of response to FDA's request for revised Part 1 study design.
16.	Appendix U CARTOX Guidelines for the Management of CRS and ICANS	Added CARTOX Guidelines appendix.	Change made for investigator convenience.

Signature Page for TAK-007-2001 Protocol Amend 5
Title: TAK-007-2001 Protocol Amend 5

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