

CLINICAL STUDY PROTOCOL

**A Phase Ib/II Clinical Study of Fully Human BCMA Chimeric Antigen
Receptor Autologous T Cell Injection (CT103A) in the Treatment of
Patients with Relapsed/Refractory Multiple Myeloma**

Sponsor:	Nanjing IASO Medical Technology Co., Ltd.
Protocol Number:	XL-LCYJ-0007
Protocol Version:	5.0
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Sponsor's Statement

I will conscientiously fulfill the responsibilities of the sponsor according to International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki and all applicable government regulations. I will fulfill the responsibilities of the sponsor including initiation, monitoring, and funding of this trial. I agree to conduct this clinical study in accordance with the design and provisions in the protocol.

Signature of Responsible Party

Date (dd/mm/yyyy)

Nanjing IASO Medical Technology Co., Ltd.

Sponsor

Investigator's Statement

I, the undersigned, have reviewed this protocol entitled: "A Phase Ib/II Clinical Study of Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A) in the Treatment of Patients with Relapsed/Refractory Multiple Myeloma" and the Investigator's Brochure and I agree to conduct this protocol in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki, and all applicable government regulations. This protocol will be carried out upon the approval from the Ethics Committee (EC) or Institutional Review Board (IRB).

I understand that the protocol may not be modified without written approval of the sponsor and that all changes to the protocol must be submitted to the applicable regulatory authorities and the EC/IRB prior to implementation. The exception is measures required to eliminate immediate hazard(s) to the subject. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from sponsor.

Principal Investigator

Date (dd/mm/yyyy)

Institution

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List of Abbreviation

Abbreviation	Definition
AE	Adverse Event
AESI	Averse Events of Special Interest
ALB	Albumin
ALC	Absolute lymphocyte count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
ASBMT	American Society for Blood and Marrow Transplantation
ASCT	Autologous Stem Cell Transplantation
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
ASTCT	American Society of Transplantation and Cellular Therapy
AUC	Area Under the Curve
AUC _{0~28d}	Area Under the Curve from 0 to day 28
AUC _{0~90d}	Area Under the Curve from 0 to day 90
BCMA	B-Cell Maturation Antigen
BCR	B Cell Receptor
BiPAP	Bilevel Positive Airway Pressure
BUN	Blood Ure Nitrogen
CAR	Chimeric Antigen Receptor
CD	Cluster of Differentiation
CDE	Center For Drug Evaluation
CI	Confidence Interval
CK	Creatine Kinase
C _{max}	Maximum Concentration

Abbreviation	Definition
CMV	Cytomegalovirus
CPAP	Continuous Positive Airway Pressure
CR	Complete Response
CRA	Clinical Research Associate
CRAB	Calcium elevation, Renal failure, Anemia, Lytic bone lesions
CRE	Creatinine
CRES	CAR-T cell Related Encephalopathy Syndrome
CRF	Case Report Form
CRP	C-reactive protein
CRR	Complete Remission Rate
CRRT	Continuous Renal Replacement Therapy
CRS	Cytokine Release Syndrome
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBIL	Direct Bilirubin
DIC	Disseminated Intravascular Coagulation
DLBCL	Diffuse Large B-Cell Lymphoma
DLI	Donor Lymphocyte Infusion
DLT	Dose-Limiting Toxicity
DM	Data Management
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram

Abbreviation	Definition
EDC	Electronic Data Capture System
ESBL	Extended-Spectrum -Lactamases -
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FIB	Fibrinogen
FISH	Fluorescence in Situ Hybridization
FLC	Free Immunoglobulin Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GVHD	Graft-Versus-Host Disease
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic Lymphohistiocytosis
HSCT	Hematopoietic Stem Cell Transplantation
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
ID	Identifier
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IIT	Investigator-Initiated Trial

Abbreviation	Definition
IL	Interleukin
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IPA	Invasive Pulmonary Aspergillosis
IRC	Independent Review Committee
IV	Intravenous
IVIG	Intravenous immunoglobulin
LDH	Lactic Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAS	Macrophage Activation Syndrome
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGF	New Generation Flow
NHL	Non-Hodgkins Lymphoma
NMPA	National Medical Products Administration
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PCT	Procalcitonin
PD	Pharmacodynamics
PFS	Progression Free Survival

Abbreviation	Definition
PI	Principle Investigator
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
Q-PCR	Quantitative Polymerase Chain Reaction
QTcF	Fridericia QT
RCL	Replication Competent lentivirus
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
RRMM	Relapsed and Refractory Multiple Myeloma
SAE	Serious Adverse Event
scFv	Single-Chain Fragment Variable
sCR	Stringent Complete Response
SOP	Standard Operating Procedure
SPD	Sum of Products of greatest Diameters
TBIL	Total Bilirubin
TLS	Tumor Lysis Syndrome
T _{max}	Time of maximum concentration
TP	Total Protein
TRAE	Treatment Related Adverse Events
TT	Thrombin Time
TTR	Time To Response
ULN	Upper Limit of Normal
VCN	Vector Copy Number
VGPR	Very Good Partial Response
WBC	White Blood Cell
WHO	World Health Organization

Protocol Amendment		
Amendment	Protocol version	Version date
Original version	1.0	May 1, 2019
Amendment 1	2.0	August 26, 2019
Amendment 2	3.0	September 30, 2019
Amendment 3	3.1	November 07, 2019
Amendment 4	3.2	March 02, 2020
Amendment 5	4.0	December 08, 2020
Amendment 6	4.1	September 10, 2021
Amendment 7	5.0	June 17, 2022

Amendment 7 (June 17, 2022)

Overall Rationale for the Amendment: The sponsor contacted the regulatory authority prior to submitting the conditional marketing application. The regulatory authority requested a bridging study to confirm the clinical efficacy and safety of the investigational product (IP) due to the change in manufacturing site following approval. The study design was revised to accurately reflect the bridging study, and updates were made to the sample size and study status. Other changes are outlined below:

Applicable Section(s)	Description of Change(s)
Synopsis 3. Study Design	The study design and sample size were updated due to changes in the manufacturing site.
1.1 Disease background	Treatment options for multiple relapses were added in the background section according to the “Guidelines for the diagnosis and management of multiple myeloma in China (2022 revision)”.
1.2 Summary of Non-clinical Findings	The summary of non-clinical findings was updated.
1.3.1 XL-LCYJ-0003 study	The clinical data for the XL-LCYJ-0003 study was updated with the new cut-off date of June 30, 2021.
5.8 Long-term follow-up period	Updated the description of the long-term follow-up period to include long-term follow-up and post-dropout follow-up. Added information on carcinogenic or mutagenic drugs that should

Applicable Section(s)	Description of Change(s)
	also be collected during the long-term follow-up period.
5.7.2 Post-treatment follow-up period	Updated a detailed description of the time interval for lentiviral genomic insertion site assay according to the newly published “Technical Guidelines for Long-Term Follow-up Clinical Studies of Gene Therapy Products”.
5.9 Dropout/End of study 5.9.1 Dropout	Clarified the definition of dropout/End-of-study for clarification. Added the statement, “Bone marrow aspiration/biopsy test may not be required if blood and urine tests show no signs of disease progression” to the bone marrow aspiration/biopsy section.
6.6 RCL	Updated the timepoints for RCL and VCN testing in long-term follow-up.
7.3 Adverse Drug Reaction (ADR)	Added definition of adverse drug reaction (ADR).
7.5.3 Recording of Adverse Events	Revised the rules for recording adverse events: The investigator must use medical terminology and avoid colloquialisms and abbreviations when recording adverse events (AEs). If a diagnosis is available, it should be recorded as the AE instead of individual signs and symptoms. However, if a diagnosis is not available at the time of reporting, each sign and symptom should be recorded. Subsequent diagnoses, if established, should be reported as follow-up information. In general, adverse events should record the primary event, unless the secondary event is severe (usually $\geq$ grade 3) or a serious adverse event. If the relationship between events is unclear, they should be recorded separately.
7.6.3 Expectedness Assessment of Adverse Events	Added description of how to evaluate the expectation of adverse events.
7.10 Abnormal Laboratory Values	Updated that abnormal laboratory values should be recorded as adverse events if they are clinically significant.

Amendment 6 (September 10, 2021)

Overall Rationale for the Amendment: The inclusion criteria were revised and allowed for subjects who have received CAR-T therapy as a last-line treatment, without

limiting the progression to 12 months. The criteria for measurable lesions in the eligible population have been updated based on communication with regulatory authorities. The available drugs for bridging therapy have been specified, and the use of anti-CD38 monoclonal antibody is not acceptable. Specified changes are outlined below:

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, and spelling errors were noted and revised.
Synopsis 2. Objectives and Endpoints	The exploratory objective endpoints no longer include an analysis of inflammatory factors (To explore the relevance of inflammatory factors to clinical safety and efficacy) as it was already included in the PD analysis in the secondary objectives.
Synopsis 3.1.2 Sites	Updated the number of sites for the Phase II trial from 11 to 14 to reflect the actual situation.
Synopsis 3.2.1 Inclusion Criteria	Revised inclusion criteria for progression time after last line therapy based on clinical realities. The following statement has been updated: Documented disease progression during or within 12 months of the last anti-myeloma treatment (the progression for subjects whose last line treatment was CAR-T therapy was not limited to 12 months post-treatment). Revised eligibility criteria based on communications with the regulatory agency: Serum M protein level: IgG type M protein ≥ 10 g/L, or IgA, IgD, IgE, IgM type M protein ≥ 5 g/L.
Synopsis 3.2.2 Exclusion Criteria	Language was added to clarify that the exclusion criteria include a percentage of plasma cells ($\geq 5\%$) in peripheral blood. Revised the exclusion criteria based on clinical realities and modified the washout time for subjects who received interventional clinical trial drugs prior to signing the ICF to protect the rights and interests of the subjects. Updated the toxicities from prior therapies according the clinical situation: Non-hematologic toxicities from previous anti-myeloma therapy have not recovered to baseline or grade ≤ 1 (NCI-CTCAE v5.0, except for alopecia and grade 2 peripheral neuropathy).
Synopsis 4.1.3 Bridging therapy	Revised description of bridging therapy with anti-CD38 monoclonal antibody not acceptable.
Schedule of Activities	Revisions to expand the visit timeframe window in long-term follow-

Applicable Section(s)	Description of Change(s)
	up period. Specified per clinical practice that the oxygen saturation tests should be performed at least twice with a time interval of at least 6 hours from cell infusion to discharge from the hospital. Specified that the temperature should be tested at least twice with a time interval of at least 6 hours from cell infusion to D28 to ensure subject safety. Specified that the blood pressure should be tested at least twice with a time interval of at least 6 hours during CRS. Added that the “Bone marrow aspiration/biopsy is required at post-infusion follow-up visits if the subject has achieved $\geq$ VGPR or disease progression, and at other follow-up visits as deemed necessary by the investigator” to minimize invasive examinations. The following statements were added to modify the requirements for lymphodepletion chemotherapy to facilitate clinical implementation while ensuring subject safety and the potential efficacy of the clinical trial: Baseline assessment (pre-lymphodepletion assessment) should be performed within 7 days prior to the lymphodepletion, except that the vital signs and physical examination should be performed within 1 day prior to the lymphodepletion. Pre-lymphodepletion assessment requires that the subject has not achieved a complete response (CR), this assessment may be confirmed by local laboratory results, but central laboratory results which are considered as baselines should be completed at the same time. Baseline tumor burden assessment within 14 days prior to the start of lymphodepletion are acceptable, except for the bone marrow aspiration/biopsy-related assessments within 4 weeks are acceptable. Prior to lymphodepletion, the appropriate tests should be repeated to confirm that subjects meet the criteria for lymphodepletion.
Schedule of Activities 3.2.5 Criteria for lymphodepletion	Added the criteria of peripheral plasma cell percentage < 10% prior to lymphodepletion.
3.3.2 Dropout/ End of Study 5.9 Dropout/End of study	Added the definition of “Dropout” and “End of Study” for clarification.
Schedule of Activities	Emphasized the need for two consecutive tests to confirm the efficacy

Applicable Section(s)	Description of Change(s)
6.2.2 Efficacy Assessment Criteria	assessment.
5.1.1 Screening Period	Clarified that the same subject may only receive one repeat test or re-screening.
5.7.2 Post-treatment follow-up period	Specified the timepoints that lentiviral genomic insertion site assay should be performed post-infusion.
7.11 Adverse Events of Special Interest	Added the tumor lysis syndrome as an AESI.
10.5.4 Analysis of Efficacy Measurements	Added the parameters of the time to complete response and the duration of MRD negativity in efficacy assessment.
24.2 Appendix 2 Response Assessment of Multiple Myeloma-Revised IMWG Criteria	Added that “For IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments” per IMWG 2016 for clarify.

Amendment 5 (December 08, 2020)

Overall Rationale for the Amendment: The protocol was revised to evaluate the efficacy and safety of eque-cel in a Phase II study following communication between the sponsors and the regulatory authority. The adverse events, serious adverse events, and SUSAR sections have been updated according to the latest version of GCP. The specific changes are as follows:

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, and spelling errors were noted and revised.
Synopsis Exclusion/exclusion criteria	Added that patients should not receive supportive treatment within 7 days prior to screening. The criterion of creatinine for screening was removed, and only creatinine clearance (CrCl) calculated by the Cockcroft-Gault Formula has been left to reflect the renal function. The definition of the therapeutic dose of glucocorticoids was added for clarification. Patients with plasma cell leukemia was excluded based on the previous study data.

Applicable Section(s)	Description of Change(s)
	A new exclusion criterion was added, which states that extramedullary lesions are not allowed, excepted for a single paramedullary extramedullary lesion with a maximum transverse diameter of ≤ 3 cm. New exclusion criterion of having central nervous system diseases was added.
Synopsis	Revised the language of primary and secondary objectives and added exploratory objectives.
Synopsis Study design	The study design was revised based on communication between sponsors and regulatory authority. Endpoints for evaluating the efficacy by independent review committee, evaluating the immunogenicity of CT103A, and monitoring the generation of replication competent lentivirus (RCL) were added after the sponsor-regulatory authority communication. The sample size and safety/efficacy analysis parameters for the pivotal study were recalculated and revised after the meeting. Revised the age inclusion criteria from “over 18 years old” to “Greater than or equal to 18 years of age and less than or equal to age 70” to ensure the safety of older patients. Updated the criteria for lymphodepletion and eque-cel infusion to maximize the benefit-risk ratio.
Synopsis 3.2.4 Criteria for apheresis 5.2 Apheresis	Updates were made to the tests based on the apheresis criteria, and the PBMC collection requirements were adjusted according to clinical practice and historical data on cell preparation.
Synopsis 4.1.3 Bridging therapy	To ensure sufficient washout time for the bridging therapy medication and to minimize its effects on the baseline results, at least 7 days were added between bridging therapy and pre-lymphodepletion.
Schedule of activities	Deletions were made on the PK sample collection timepoints based on previous study data. It was specified that the temperature should be tested at least twice (time interval ≥ 6h) from cell in fusion to D28 to safeguard subjects. Some sample collection timepoints were updated based on previous data.
7. Adverse Events and Serious Adverse Events	Updated the definition of adverse events and serious adverse events in accordance with the latest GCP.

Applicable Section(s)	Description of Change(s)
	The outcome of adverse events, as well as the start and end timepoints of AE/SAE collection and recording, have been revised in accordance with the latest GCP. An explanation of AE expectedness assessment has been added for investigators' reference. The definition and detailed description of Suspected Unexpected Serious Adverse Reaction (SUSAR) have been added, as well as a detailed description of Adverse Events of Special Interest (AESI). Added description of new cancers and clarified that new cancers should be considered as SAEs. The report of SAE and the follow-up of AE/SAE has been updated according to the latest GCP.
8. Pregnancy	The description of pregnancy has been updated in accordance with the latest GCP. The observation period for pregnancy has been revised to two years.
10. Statistical Analysis 10.4 Analysis Population	Added the description to clarify the interim analysis and final analysis. Added the screened analysis set, enrolled analysis set (EAS), apheresis analysis set and lymphodepleting pretreatment analysis set.
12. Data Monitoring Committee (DMC)	Revision was made to the data monitoring committee, which was established in this study.
14. New Drug Application Plan	The New Drug Application Plan was added as required after communication between sponsors and regulatory authorities.
24.4.2 Immune Effector Cell-associated Neurotoxicity Syndrome (CANS)	Revised the recommendations on CRS and ICANS managements based on the NCCN 2020 guideline.
24.5 Appendix	Specify the prior lines of therapy for multiple myeloma according to the "Guidelines for determination of the number of prior lines of therapy in multiple myeloma".

Amendment 4 (March 02, 2020)

Overall Rationale for the Amendment: The dose of cyclophosphamide used in the previous investigator-initiated trial was 20 mg/kg/day, equivalent to 800 mg/m²/day. However, this higher dose resulted in a higher frequency of adverse effects, particularly

myelosuppression. To minimize the risks to enrolled subjects, the dose of cyclophosphamide was reduced to 500mg/m²/day, which is consistent with other CAR-T trials. The changes are as follows:

Applicable Section(s)	Description of Change(s)
Synopsis 3. Study Design	To compare safety and preliminary efficacy data, and determine the recommended phase 2 dose (RP2D), the number of enrolled cases was increased to a range of 6-20 subjects. To evaluate the integration of oncogenic DNA viruses into the human genome, the lentiviral genomic insertion site assay was added. To avoid unnecessary invasive tests, the updated requirement for pre-lymphodepletion states that the bone marrow assessment may not be conducted within 7 days prior to lymphodepletion, at the investigator's discretion.
Synopsis Lymphodepleting chemotherapy	To minimize the adverse events and risks, the dosage of cyclophosphamide was adjusted from 20 mg/kg/day to 500mg/m ² /day.
Schedule of activity	The decision to remove MRD NGS testing was made due to the lack of standardized testing criteria. The PK sample should be collected along with a routine hematology test to detect the absolute lymphocyte count in the peripheral blood. This count is used to calculate the CAR-T cells.
4.3.2 Permitted Concomitant Treatments	The starting time to collect concomitant treatments was changed from the IP administration to apheresis.

Amendment 3 (November 07, 2019)

Overall Rationale for the Amendment: The protocol was revised according to the Ethics Committee's suggestions to enhance the safety of enrolled subjects, extend the duration of safety data collection, and improve the feasibility of project implementation. The specific changes are outlined below:

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, and spelling errors were noted and revised.

Applicable Section(s)	Description of Change(s)
Synopsis 3. Study Design	For safety reasons, the infusion interval is adjusted as follows: "The infusion interval for the first three subjects in the low-dose group is 14 days, while the infusion interval for each subject in the high-dose group is also 14 days".
Synopsis 2.2 Endpoints	The Phase II secondary endpoints were rearranged to include safety endpoints such as the incidence and severity of adverse events (per NCI-CTCAE v5.0), the incidence and severity of CRS and ICANS (per ASTCT 2019 criteria), changes in laboratory test results, vital signs, and physical examination.
Schedule of Activities	Updated anti-drug antibody (ADA) visit timepoints based on preliminary study results. The RCL tests were rearranged for up to 15 years, as required by the regulatory authority.
Synopsis 3. Study Design	The criteria for hypertension have been updated according to the latest guideline.

Amendment 2 (September 30, 2019)

Overall Rationale for the Amendment: The Phase Ib dose group was expanded to include a lower dose of 0.5×10^6 CAR-T cells/kg to evaluate its efficacy and safety. This decision was based on the preliminary study data, which showed that the ORR of the 1.0×10^6 CAR-T cells/kg dose level was 100%. The specific changes made were as follows:

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, and spelling errors were noted and revised.
Synopsis 2. Objectives and Endpoints	The primary objective of the Phase Ib study is safety, therefore the primary objective has been revised to "To evaluate the safety of different dose levels of CT103A in the treatment of patients with RRMM and to confirm the RP2D. Efficacy is the secondary objective of the Phase Ib study. The statement of the secondary objective "To evaluate the efficacy of CT103A in the treatment of patients with RRMM" has been added. To provide a comprehensive view of the response depth after treatment and to improve the predictability of long-term outcomes, the secondary endpoints "MRD assessment: sustained MRD

Applicable Section(s)	Description of Change(s)
	negative, NGS MRD negative, NGF MRD negative, and imaging MRD negative" were added.
Synopsis 3. Study Design	To further evaluate the efficacy and safety of a lower dose level, 0.5×10^6 CAR-T cells/kg was added to Phase 1b in the study design. To ensure subject safety, the first three subjects enrolled in the newly initiated sites should be observed for at least 14 days before enrolling more patients. The rationale for determining the final sample size included consideration of the dropout rate, and the sample size has been calculated accordingly.
Synopsis 3.2.1 Inclusion criteria	The target (BCMA) of the CT103A was required to be positively expressed on the surface of plasma cell membranes, as detected by immunohistochemistry (IHC) or flow cytometry. To reduce reproductive risk, the subject and spouse must use effective contraception methods from ICF signing until one year post-infusion. To protect the rights of the subjects, the inclusion criteria "Subjects must personally sign an informed consent form approved by the ethics committee" is added.
Synopsis 3.2.2 Exclusion criteria	Based on the preliminary results of the exploratory study, it was found that RRMM patients with extramedullary lesions did not have a favorable outcome and therefore they were excluded from the study. Consequently, the exclusion criterion "RRMM patients with extramedullary lesions only" was added. To protect subject compliance and avoid confounding the safety analysis results, the exclusion criterion "Suspected or confirmed central nervous system involvement." was added.
Synopsis 4.1.3 Bridging therapy	To ensure the patients' well-being, bridging therapy was added as necessary to stabilize patients' disease condition between apheresis and lymphodepletion chemotherapy.
Schedule of Activities 5.3 Baseline Assessment Visit	To ensure the accuracy of the subsequent efficacy evaluation, tumor burden evaluation and 12-lead electrocardiography were added at the pre-lymphodepletion visit.

Amendment 1 (August 26, 2019)

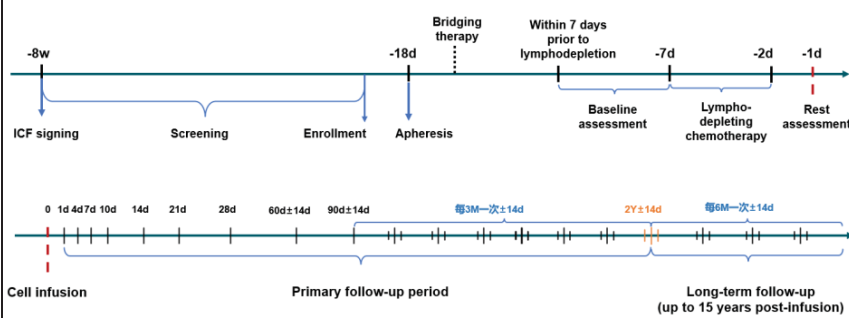
Overall Rationale for the Amendment: The first version is for internal use only and

has been updated to version 2 based on internal discussions. Version 2 is intended for Investigational New Drug applications only and has not been submitted to ECs.

Synopsis

Protocol No.	XL-LCYJ-0007
Investigational product (IP)	Fully human-derived BCMA chimeric antigen receptor (CAR) autologous T-cell injection (CT103A)
Title	A Phase Ib/II Clinical Study of Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A) in the Treatment of Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
Sponsor	Nanjing IASO Medical Technology Co., Ltd.
Phase	Phase Ib/II
Sites	Phase I: 7 sites Phase II: 14 sites
Objectives	<u>Phase I</u> Primary objectives: - To evaluate the safety of CT103A at the recommended phase II dose (RP2D) Secondary objectives: - To evaluate the efficacy of CT103A in the treatment of patients with RRMM - To evaluate the pharmacokinetic (PK) characteristics of CT103A - To evaluate the pharmacodynamic (PD) characteristics of CT103A Exploratory objectives: - To evaluate the immunogenicity of CT103A - To monitor the generation of replication competent lentivirus (RCL) <u>Phase II:</u> Primary objectives: - To evaluate the efficacy of CT103A in the treatment of patients with RRMM Secondary objectives: - To evaluate the safety of CT103A in the treatment of patients with RRMM - To evaluate the pharmacokinetic (PK) characteristics of CT103A - To evaluate the pharmacodynamic (PD) characteristics of CT103A Exploratory objectives:

	- To evaluate the immunogenicity of CT103A - To monitor the generation of replication competent lentivirus (RCL)
Study Design	This study was designed in accordance with the requirements of the Chinese Good Clinical Practice (GCP) and the "Technical Guidelines for the Research and Evaluation of Cell Therapy Products" and other regulatory guidelines, and was optimized based on the "Considerations for the Design of Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy for Malignant Tumors of the Hematopoietic System" and "Technical Guidelines for Conditional Approval of Drugs (Trial)" issued by the Clinical Department of the Center for Drug Evaluation (CDE) for biological products. In an investigator-initiated, non-registered clinical trial of CT103A using a "3+3" dose escalation design for the treatment of RRMM patients (see Section 1.3 for details), a total of 12 subjects were enrolled and received three dose levels of CT103A injection, including 1.0×10^6 CAR-T cells/kg ($n = 3$), 3.0×10^6 CAR-T cells/kg ($n = 3$), and 6.0×10^6 CAR-T cells/kg ($n = 3$). No dose-limiting toxicity (DLT) was observed in the 1.0×10^6 and 3.0×10^6 CAR-T cells/kg dose groups. Only one case of DLT was observed in the 6.0×10^6 CAR-T cells/kg dose group, which was grade 4 CRS. Through further expansion studies of 11 subjects who received 1.0×10^6 CAR-T cells/kg ($n = 6$) and lower doses of 0.5×10^6 CAR-T cells/kg ($n = 5$), the safety, efficacy, PK, and PD of the dose escalation and expansion phases were comprehensively analyzed and 1.0×10^6 CAR-T cells/kg was identified as the recommended phase II dose (RP2D) for CT103A. In this study, a dose-expansion (phase I) study was first planned to further evaluate the safety and efficacy of CT103A injection at the RP2D dose level in patients with RRMM. Then, based on the preliminary results of the dose-expansion phase (phase I), the investigator and sponsor will communicate with the CDE to conduct a pivotal phase II clinical study to fully evaluate the efficacy and safety of CT103A injection at the RP2D dose. During the phase II study, the sponsor communicated with the CDE prior to submitting a conditional marketing application, as the manufacturing site will change after marketing. The CDE required that a bridging study should be conducted during the phase II study to confirm the clinical efficacy and safety of the investigational product after the change in manufacturing sites. Overview of the Phase I Study Design: The Phase I study is a multi-center, open-label, dose-expansion study designed to evaluate the safety, PK and PD characteristics, and immunogenicity of the IP at the RP2D level, and to preliminarily observe the efficacy of CT103A in a small number of subjects with RRMM to provide a basis for the Phase II study. Seven sites were selected for the Phase I study. After signing the informed consent form (ICF), eligible subjects received CT103A at the dose of 1.0×10^6 CAR-T

	cells/kg. This study was designed to enroll 6-20 subjects, with a total of 20 subjects were enrolled and 17 subjects received CT103A. After all subjects completed the 1-month post-infusion safety evaluation, the sponsor communicated with the CDE based on the available safety, efficacy, and PK data, and conducted the Phase II study after the communication. Overview of the Phase II Study Design: The Phase II study will continue to enroll eligible subjects at the RP2D dose level (1.0×10^6 CAR-T cells/kg) established in the Phase I study, to confirm the efficacy and safety of the RP2D dose in RRMM patients. This study plans to enroll at least 109 subjects at the RP2D dose level (including the 17 subjects who completed in Phase I, 78 subjects who completed in Phase II, and at least 14 subjects intended for the bridging study). Subjects meeting the inclusion criteria but not the exclusion criteria will receive a single dose of CT103A at the recommended dose level (1.0×10^6 CAR-T cells/kg). The study plans to follow all subjects for safety and efficacy until withdrawal of informed consent, withdrawal from the study, death, loss to follow up, or end of study, whichever occurs first. Subjects who drop out will continue to be followed until study completion. Study procedure The study includes screening and enrollment, apheresis, bridging therapy, baseline assessment (pre-lymphodepletion assessment), lymphodepleting chemotherapy, rest assessment, cell infusion, primary follow-up period, and long-term follow-up period.  For newly initiated sites, there should be at least 14 days between infusions of the first three subjects.
Sample size	Phase I study: - The enrollment has been completed, and a total of 17 subjects have received cell infusion. Phase II study: - Confirmatory study: The hypothesis test is based on whether the ORR at 3 months is greater than 35% (i.e., $H_0: p \leq 0.35$ vs $H_1: p > 0.35$).

	Therefore, assuming the 3-month ORR is 60% in the full analysis set (FAS), with a one-sided $\alpha = 0.025$, at least 53 subjects in the FAS are required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis. In this stage, 78 subjects have received cell infusion; • Bridging study: The hypothesis test is based on whether the ORR at 3 months is greater than 35% (i.e., $H_0: p \leq 0.35$ vs $H_1: p > 0.35$). Combined with the results of the confirmatory study, the 3-month ORR in the FAS is expected to be 80% with a one-sided $\alpha = 0.025$. Therefore, a minimum of 14 subjects in the FAS population is required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis; • Therefore, at least 109 subjects are required to complete the CT103A infusion in this study. However, considering a 10% drop-out rate between enrollment and infusion, it is expected that a total of 120 to 125 subjects meeting the inclusion criteria are expected to be enrolled.
Study duration	This study is divided into a primary follow-up period and a long-term follow-up period. This study started in 2019, and the primary follow-up period is assumed to last for 4-5 years.
Study population	Subjects must meet all the following inclusion criteria and none of the exclusion criteria: <u>Inclusion Criteria:</u> 1. Greater than or equal to 18 years of age and less than or equal to age 70. 2. Documented diagnosis of multiple myeloma according to the IMWG diagnostic criteria; have received at least 3 prior lines of therapy, including proteasome inhibitor (PI) and immunomodulatory-based (IMiD) chemotherapy; documented disease progression during or within 12 months of the last anti-myeloma treatment (the progression for subjects whose last line treatment was CAR-T therapy was not limited to 12 months post-treatment). 3. Positive BCMA expression on tumor cells by immunohistochemistry (IHC) or flow cytometry is required prior to enrollment. 4. Presence of measurable lesion at screening as determined by any of the following criteria: • The proportion of primitive or monoclonal plasma cells $\geq 5\%$ by bone marrow cytology, bone marrow biopsy immunohistochemistry, or flow cytometry;

	• Serum M protein level: IgG type M protein ≥ 10 g/L, or IgA, IgD, IgE, IgM type M protein ≥ 5 g/L; • Urine M protein level ≥ 200 mg/24h; • Light chain multiple myeloma without measurable lesions in serum or urine: Involved serum free light chain ≥ 100 mg/L and abnormal serum κ/λ free light chain ratio. 5. ECOG score of 0 or 1 (refer to Appendix 1) 6. Expected survival time is greater than or equal to 12 weeks. 7. Subjects must have adequate organ function and meet all of the following laboratory values prior to enrollment: • Hematology: Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$ (supportive growth factor is permitted, but must be without supportive treatment within 7 days prior to laboratory testing); absolute lymphocyte count (ALC) $\geq 0.3 \times 10^9/L$; platelet count $\geq 50 \times 10^9/L$ (must be without supportive blood transfusion within 7 days prior to laboratory testing); hemoglobin ≥ 60 g/L (without red blood cell [RBC] transfusion within 7 days prior to laboratory testing; the use of recombinant human erythropoietin is permitted); • Liver function: Alanine transaminase (ALT) and aspartate transaminase (AST) $\leq 2.5 \times$ upper limit of normal (ULN); serum total bilirubin $\leq 1.5 \times$ ULN; • Renal function: Creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula ≥ 40 ml/min; $\text{CrCl} = (140 - \text{Age}) \times \text{Mass (kg)} \times [0.85 \text{ if female}] / 72 \times [\text{Serum Creatinine (mg/dL)}]$ • Coagulation function: Fibrinogen ≥ 1.0 g/L, activated partial thromboplastin time (APTT) $\leq 1.5 \times$ ULN, prothrombin time (PT) $\leq 1.5 \times$ ULN; • Oxygen saturation $\geq 91\%$; • Left ventricular ejection fraction (LVEF) $\geq 50\%$. 8. Female subjects of childbearing potential or male subjects with a partner of childbearing potential agree to use effective contraception methods from ICF signing until one year after CAR-T cell infusion. 9. The subject must personally sign an informed consent form approved by the ethics committee. <u>Exclusion Criteria:</u> 1. Subjects with graft-versus-host-disease (GVHD) or those requiring long-term use of immunosuppressants.
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	2. Received autologous hematopoietic stem cell transplantation (Auto-HSCT) within 12 weeks prior to apheresis, received twice Auto-HSCT, received prior allogeneic hematopoietic stem cell transplantation (Allo-HSCT). 3. There are not enough peripheral blood mononuclear cells available for CAR-T cell manufacturing. 4. Received prior anti-myeloma therapies as follows: • Treatment with monoclonal antibodies within 21 days prior to apheresis, or • Treatment with cytotoxic chemotherapy or proteasome inhibitor within 14 days prior to apheresis, or • Treatment with immunomodulator within 7 days prior to apheresis, or • Anti-myeloma therapies other than those described above within 14 days or at least 5 half-lives (whichever is longer) prior to apheresis. 5. Use of glucocorticoids (defined as prednisone or equivalent > 20 mg/day) at a therapeutic dose within 7 days prior to apheresis. Physiologic replacement, topical, and inhaled steroids are permitted, nevertheless. 6. Uncontrolled hypertension under medical therapy. 7. Severe heart disease: Including but not limited to unstable angina, myocardial infarction (within 6 months prior to screening), congestive cardiac failure (New York Heart Association [NYHA] classification grade $\geq$ III), severe arrhythmia. 8. Unstable systemic disease as judged by the investigator: Including but not limited to severe hepatic, renal, or metabolic disease requiring therapy. 9. Malignancies other than multiple myeloma within 5 years prior to screening, excluding adequately treated cervical carcinoma in situ, basal or squamous epithelial cell skin cancer, localized prostate cancer after radical surgery, ductal carcinoma in situ of the breast after radical surgery. 10. History of organ transplantation. 11. Suspected or confirmed central nervous system involvement. 12. Have extramedullary lesions (except for a single paramedullary extramedullary lesion with maximum transverse diameter ≤ 3 cm). 13. Plasma cell leukemia ($\geq 5\%$ plasma cells in peripheral blood). 14. Major surgery within 2 weeks prior to apheresis, or planned surgery within 2 weeks after CT103A infusion (subjects planning to receive surgery under local anesthesia are permitted to be enrolled in this study). 15. Treated with other investigational products within 1 month prior to signing the informed consent form (ICF).
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	16. Uncontrollable active infection (excluding CTCAE grade 2 urinary and respiratory tract infections) within 7 days prior to apheresis. 17. Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with detectable hepatitis B virus (HBV) DNA in peripheral blood; positive hepatitis C virus (HCV) antibody with positive HCV RNA in peripheral blood; positive human immunodeficiency virus (HIV) antibody; positive cytomegalovirus (CMV) DNA; positive syphilis test. 18. Pregnant or breastfeeding women; 19. Have psychiatric disorders, conscious disorders, or central nervous system diseases; 20. Non-hematological toxicities from previous anti-myeloma therapy have not recovered to baseline or grade ≤ 1 (NCI-CTCAE v5.0, except for alopecia and grade 2 peripheral neuropathy). 21. Any condition for which, at the discretion of investigators, participation would not be in the best interest of the subject. Subjects must meet the following criteria prior to apheresis: (1) The following requirements must be met within 1 day prior to apheresis: - Hematology: Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$; absolute lymphocyte count (ALC) $\geq 0.3 \times 10^9/L$; platelet count $\geq 50 \times 10^9/L$; hemoglobin ≥ 60 g/L; must be without supportive treatment within 7 days prior to the above tests. (2) The following requirements must be met within 7 days prior to apheresis: - Coagulation function: Fibrinogen ≥ 1.0 g/L, activated partial thromboplastin time (APTT) $\leq 1.5 \times \text{ULN}$, prothrombin time (PT) $\leq 1.5 \times \text{ULN}$; (3) Not treated with systemic steroids (other than inhaled or topical use) within 14 days prior to apheresis; (4) The subject does not meet the exclusion criteria 2), 4), 14) and 16) as reconfirmed; (5) There are no other conditions that, at the discretion of investigators, make the subjects unsuitable for apheresis. Subjects must complete the pre-lymphodepletion assessment prior to initiation of lymphodepleting chemotherapy and meet the following criteria: (1) If a subject receives bridging therapy after apheresis, the bridging therapy must have been completed ≥ 7 days prior to the pre-lymphodepletion assessment without achieving a complete response (CR) as assessed by the investigator;
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	(2) Absence of severe active infection as determined by the investigator (< grade 2 genitourinary infections and upper respiratory tract infections are excluded); (3) Axillary body temperature should be $\leq 38^{\circ}\text{C}$ within 48 hours prior to lymphodepleting chemotherapy; (4) Subjects must meet the following requirements within 7 days prior to the lymphodepleting chemotherapy: • Oxygen saturation $> 91\%$; • Left ventricular ejection fraction (LVEF) $\geq 50\%$; (5) Peripheral plasma cell percentage $< 10\%$; (6) Lymphodepletion treatment may be administered after investigator assessment of hematology, hepatic and renal function, and coagulation; (7) There are no other conditions that, at the discretion of investigators, make the subjects unsuitable for apheresis. Subjects must meet the following criteria prior to CT103A infusion: (1) Absence of severe active infection as determined by the investigator (< grade 2 genitourinary infections and upper respiratory tract infections are excluded); (2) Axillary body temperature should be $\leq 38^{\circ}\text{C}$ within 48 hours prior to cell infusion; (3) Subjects should not receive glucocorticoids at a therapeutic dose (defined as prednisone or equivalent $> 20 \text{ mg/day}$) and other immunosuppressants within 72 hours prior to CT103A infusion; (4) Oxygen saturation $> 91\%$; (5) There are no other conditions which, at the discretion of investigators, make the subjects unsuitable for apheresis.
Bridging therapy; Lympho-depleting chemotherapy; Investigational product	Bridging therapy: After apheresis and before lymphodepletion, bridging therapy may be used to maintain disease stability at the discretion of the investigator, and the decision to use bridging therapy will be made with the approval of the sponsor. Bridging therapy must be a short-term treatment previously received by the subject and should not be an anti-CD38 monoclonal antibody. Pre-lymphodepletion assessments will be performed at least 7 days after bridging therapy. Lymphodepleting chemotherapy is not allowed in subjects who have achieved CR or better according to IMWG (2016) criteria after bridging therapy. Lymphodepleting regimen Cyclophosphamide 500 mg/m^2 administered by intravenous infusion over 30 minutes daily for three consecutive days, followed by fludarabine 30 mg/m^2

	administered by intravenous infusion over 30 minutes daily for three consecutive days. If the subject has renal impairment or other conditions that require adjustment of the dose of the lymphodepleting medication, the investigator may adjust the dose of lymphodepletion drugs after comprehensive assessment and confirmation with the sponsor. Investigational product (IP): IP: CT103A injection, administered intravenously. Dose: 1.0×10^6 CAR-T cells/kg ($\pm 30\%$), a single infusion. If the manufactured CAR-T cells do not reach the planned dose but meet the criteria of $\geq 0.5 \times 10^6$ CAR-T/kg, a conditional infusion may be performed after the discussion between the investigator and the sponsor, and full evaluation of the safety of the IP and the subject's condition.
Endpoints	<u>Phase I</u> Primary endpoints: • Safety endpoints: ○ Incidence and severity of adverse events (per NCI-CTCAE v5.0); ○ Incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (per ASTCT 2019 criteria); ○ Changes in laboratory test results; ○ Vital signs and physical examination. Secondary endpoints: • Efficacy endpoints (IMWG criteria): ○ Overall response rate (ORR) at 3 months assessed by the independent review committee (IRC) and the investigator: the proportion of subjects who achieve PR or better at 3 months as defined by the International Myeloma Working Group (IMWG) response criteria; ○ Best ORR as assessed by the IRC and the investigator: the proportion of subjects who achieve PR or better as defined by the IMWG response criteria; ○ Progression-free survival (PFS) as assessed by the IRC and the investigator: Duration from the date of CT103A infusion to the date of first documented evidence of progressive disease or death due to any cause;

	- o Overall survival (OS): Duration from the start of CT103A treatment to the subject's death (due to any cause); - o Duration of response (DOR) as assessed by the IRC and the investigator: Duration from the date of the first documented response (PR or better) to the date of the first documented evidence of progressive disease, as defined by the IMWG criteria; - o Time to response (TTR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of the first documented response (PR or better); - o Time to complete response (TTCR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of first documentation of a complete response (CR) or stringent complete response (sCR); - o MRD response assessment: The proportion of subjects achieving MRD-negativity and the duration of MRD-negativity. • Pharmacokinetics (PK): The maximum concentration (C_{max}) of BCMA CAR-T cells and lentiviral vector copy number (VCN) of CT103A in peripheral blood after CT103A infusion; time to reach C_{max} (T_{max}); area under the curve (AUC) from 0 to 28 days (AUC_{0-28d}), AUC from 0 to 90 days (AUC_{0-90d}), AUC from 0 to 180 days (AUC_{0-180d}), and AUC from 0 to the last quantifiable time point; • Pharmacodynamics (PD): circulating soluble BCMA (sBCMA) in peripheral blood; cytokine and immune-related protein including CRP, IL-6 and ferritin in peripheral blood. Exploratory endpoints: • Immunogenicity: presence of human anti-CAR antibodies, and titer of confirmed positive antibodies in peripheral blood; • Presence of replication competent lentivirus (RCL) in peripheral blood. <u>Phase II:</u> Primary endpoints: • ORR at 3 months as assessed by the IRC: The proportion of subjects who achieved PR or better at 3 months as defined by the IMWG response criteria. Secondary endpoints: • Efficacy endpoints (IMWG criteria):
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	- o ORR at 3 months as assessed by the investigators: the proportion of subjects who achieved PR or better at 3 months as defined by the IMWG response criteria; - o Best ORR assessed by the IRC and the investigator: the proportion of subjects who achieved PR or better as defined by the IMWG response criteria; - o Progression-free survival (PFS) as assessed by the IRC and the investigator: Duration from the date of CT103A infusion to the date of first documented evidence of progressive disease or death due to any cause; - o Overall survival (OS): Duration from the start of CT103A treatment to the subject's death (due to any cause); - o Duration of response (DOR) assessed by the IRC and the investigator: Duration from the date of the first documented response (PR or better) to the date of first documented evidence of progressive disease, as defined by the IMWG criteria; - o Time to response (TTR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of the first documented response (PR or better); - o Time to complete response (TTCR) assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of first documentation of a complete response (CR) or stringent complete response (sCR); - o MRD response assessment: The proportion of subjects achieving MRD-negativity and the duration of MRD-negativity. • Safety endpoints: - o Incidence and severity of adverse events (per NCI-CTCAE v5.0); - o Incidence and severity of CRS and ICANS (per ASTCT 2019 criteria); - o Changes in laboratory test results; - o Vital signs and physical examination. • Pharmacokinetics (PK): The maximum concentration (C_{max}) of BCMA CAR-T cells and lentiviral vector copy number (VCN) of CT103A in peripheral blood after CT103A infusion; time to reach C_{max} (T_{max}); area under the curve (AUC) from 0 to 28 days (AUC_{0-28d}), AUC from 0 to 90 days (AUC_{0-90d}), AUC from 0 to 180 days (AUC_{0-180d}), and AUC from 0 to the last quantifiable time point;
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	- Pharmacodynamics (PD): circulating soluble BCMA (sBCMA) in peripheral blood; cytokine and immune-related protein including CRP, IL-6 and ferritin in peripheral blood. Exploratory endpoints: - Immunogenicity: presence of human anti-CAR antibodies, and titer of confirmed positive antibodies in peripheral blood; - Presence of replication competent lentivirus (RCL) in peripheral blood.
Statistical Analysis	General principles PK parameter calculations will be performed using WinNonlin 8.0 or higher, and all the other statistical analyses will be performed using SAS® 9.4 or higher. Unless otherwise specified, the summary table will be provided at planned timepoints for the study. Unplanned timepoints are generally only displayed in listings, and the listings will be categorized by variables such as subject number and assessment timepoints. For continuous variables (e.g., age), descriptive statistics of the number of observations, mean, median, quartile, standard deviation, minimum, and maximum will be presented; for categorical variables, descriptive statistics of the number and percentage for each category will be presented; geometric mean and geometric coefficient of variation will also be calculated for PK parameters such as AUC and C_{max}. The median time and its 95% confidence interval will be estimated for time-to-event data using the Kaplan-Meier method. The decimal places of the minimum and maximum are consistent with those recorded in the CRF. The mean and median are reported to 1 more decimal place than the raw data, the standard deviation is reported to 2 more decimal places than the raw data, and the percentage is rounded up to 2 decimal places. All statistics are generally rounded up to no more than 4 decimal places. With the exception of subject disposition, other statistical summary tables and graphs will be based on corresponding analysis sets, and all subjects will be presented in listings. For detailed statistical analysis methods, please refer to the Statistical Analysis Plan (SAP).

Schedule of Activities

Table 1 Schedule of Events

	Screening and enrollment ¹	Apheresis ²	Baseline assessment ³	Lympho-depletion ³	Rest assessment	CT103A Infusion ⁴	Primary follow-up period ⁵											Long-term follow-up ⁶	Dropout/End of study ⁷
	-8w~18d		Within 7 days prior to lymphodepletion	-7d~2d	-1d	0d	Hospitalization period ⁴					Post-treatment follow-up period					Every 3 months (90 days)	Every 6 months (180 days)	
							1d	4d	7d	10d	14d	21d	28d	60d	90d	± 14d			
Window									± 12h	± 12h	± 12h	± 2d	± 2d	± 14d	± 14d	± 14d	± 28d	± 14d	
Informed consent	×																		
Inclusion/Exclusion criteria ⁸	×																		
Demographics	×																		
History of tumor diagnosis and treatment	×																		
Tumor classification and staging in screening period	×																		
Non-tumor medical history ⁹	×																		
Concomitant diseases ¹⁰	×																		
Prior treatments ¹¹	×																		
Imaging-based evaluation ¹²	×		Performed if EMD is exist before infusion, or CR or disease progression is suspected.																
Echocardiography	×		×	According to clinical indications, if the subject has signs or symptoms such as heart failure.															×
Height/weight/body surface area ¹³	×	×		×	×														
Vital signs ¹⁴	×	×	×		×	×	×	×	×	×	×	×	×	×	×	×		×	
Physical examination ¹⁵	×		×		×		×	×	×	×	×	×	×	×	×	×		×	
ECOG score	×		×		×		×	×	×	×	×	×	×	×	×	×		×	
12-Lead ECG ¹⁶	×		×		×	×	×		×		×		×	×	×	×		×	

		Screening and enrollment ¹	Apheresis ²	Baseline assessment ³	Lympho-depletion ³	Rest assessment	CT103A Infusion ⁴	Primary follow-up period ⁵												Long-term follow-up ⁶	Dropout/End of study ⁷
		-8w~-18d		Within 7 days prior to lymphodepletion	-7d~-2d	-1d	0d	Hospitalization period ⁴					Post-treatment follow-up period							Every 6 months (180 days)	
								1d	4d	7d	10d	14d	21d	28d	60d	90d	Every 3 months (90 days)				
Window										± 12h	± 12h	± 12h	± 2d	± 2d	± 14d	± 14d	± 14d	± 28d	± 14d		
Safety laboratory tests	Pulse oxygen test ¹⁷	×		×		×		×	×	×	×	×	×	×							
	Blood pregnancy test ¹⁸	×	According to clinical indications, if women of childbearing potential have symptoms of suspected pregnancy such as menolipsis, vomiting, abdominal pain and vaginal hemorrhage, they should perform the test in time.																×		
	Virologic/syphilis test ¹⁹	×																	×		
	Hematology ²⁰	×	×	×		×	×	×	×	×	×	×	×	×	×	×	×		×		
	Blood biochemistry ²¹	×	×	×		×			×		×	×	×	×	×	×	×		×		
	Coagulation function ²²	×	×	×		×			×		×	×	×	×	×	×	×		×		
	Urinalysis ²³	×	×	×		×			×		×	×	×	×	×	×	×		×		
	Inflammatory factors ²⁴			×		×		×	×	×	×	×	×	×	×	×			×		
Staging and efficacy laboratory tests ²⁵	Serum calcium and calcium corrected for albumin	×		×								×		×	×	×	×	×	×		
	β2-microglobulin	×		×							×		×	×	×	×	×	×	×		
	Quantitative serum immunoglobulin test	×		×							×		×	×	×	×	×	×	×		
	Serum free light chain assay	×		×							×		×	×	×	×	×	×	×		
	Serum protein electrophoresis (SPEP)	×		×							×		×	×	×	×	×	×	×		

		Screening and enrollment ¹	Apheresis ²	Baseline assessment ³	Lympho-depletion ³	Rest assessment	CT103A Infusion ⁴	Primary follow-up period ⁵										Long-term follow-up ⁶	Dropout/End of study ⁷
		-8w~-18d		Within 7 days prior to lymphodepletion	-7d~-2d	-1d	0d	Hospitalization period ⁴					Post-treatment follow-up period					Every 6 months (180 days)	
								1d	4d	7d	10d	14d	21d	28d	60d	90d	Every 3 months (90 days)		
Window										± 12h	± 12h	± 12h	± 2d	± 2d	± 14d	± 14d	± 14d	± 28d	± 14d
	Serum immunofixation electrophoresis (SIFE)	×		×								×		×	×	×	×	×	×
	24-hour urine M-protein quantitation by electrophoresis	×		×								×		×	×	×	×	×	×
	24-hour urine free light chain assay	×		×								×		×	×	×	×	×	×
	Urine protein electrophoresis (UPEP)	×		×								×		×	×	×	×	×	×
	Urine protein immunofixation electrophoresis (UIFE)	×		×								×		×	×	×	×	×	×
Peripheral blood smear		×		×								×		×	×	×	×	×	×
Bone marrow assessment ²⁶	Cell morphology on smear	×		×								×		×	×	×	×	×	×
	Bone marrow biopsy pathology + immunohistochemistry	×		×								×		×	×	×	×	×	×
	Cytogenetics (FISH)	×																	

		Screening and enrollment ¹	Apheresis ²	Baseline assessment ³	Lympho-depletion ³	Rest assessment	CT103A Infusion ⁴	Primary follow-up period ⁵												Long-term follow-up ⁶	Dropout/End of study ⁷	
		-8w~18d		Within 7 days prior to lymphodepletion	-7d~2d	-1d	0d	Hospitalization period ⁴						Post-treatment follow-up period						Every 3 months (90 days)	Every 6 months (180 days)	
								1d	4d	7d	10d	14d	21d	28d	60d	90d	± 14d	± 14d	± 28d			
Window										± 12h	± 12h	± 12h	± 2d	± 2d	± 14d	± 14d	± 14d	± 28d	± 14d			
	Flow cytometric immunophenotyping of bone marrow (including MRD testing)	×		×								×		×	×	×	×	×	×			
Circulating soluble BCMA in peripheral blood ²⁷		×		×				×	×	×	×	×	×	×	×	×	×	×	×			
Immunogenicity ²⁸				×									×		×	×	×		×			
RCL ²⁹				×											×	×	×	×	×			
Peripheral blood samples for exploratory study ³⁰				×				×	×	×	×	×	×	×	×	×	×	×	×			
PK blood sampling	Transgene (VCN) ³²			×				×	×	×	×	×	×	×	×	×	×	×	×			
	CAR-positive T cells ³¹			×				×	×	×	×	×	×	×	×	×	×	×	×			
Apheresis			×																			
Apheresis samples for exploratory studies ³³			×																			
Genome-wide integration site detection ³⁴				×								×		×		×	×	×	×			
Lymphodepletion					×																	
Medication for prevention of infusion reactions ³⁵							×															

CT103A injection
Protocol No. XL-LCYJ-0007

	Screening and enrollment ¹	Apheresis ²	Baseline assessment ³	Lympho-depletion ³	Rest assessment	CT103A Infusion ⁴	Primary follow-up period ⁵												Long-term follow-up ⁶	Dropout/End of study ⁷
							Hospitalization period ⁴					Post-treatment follow-up period								
	-8w~18d	Within 7 days prior to lymphodepletion	-7d~2d	-1d	0d	1d	4d	7d	10d	14d	21d	28d	60d	90d	Every 3 months (90 days)	Every 6 months (180 days)				
Window								± 12h	± 12h	± 12h	± 2d	± 2d	± 14d	± 14d	± 14d	± 28d	± 14d			
CT103A cell infusion						×														
Efficacy assessment per IMWG criteria ³⁶			×							×		×	×	×	×	×	×			
Adverse event ³⁷	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×			
Serious adverse event ³⁸	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×			
Concomitant treatment ³⁹	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×			
Bridging therapy ⁴⁰		×																		
Subsequent anti-cancer treatment ⁴¹																×	×			

Note:

1. If the intervals between the ICF signing and the time of infusion exceed the intervals as specified in the protocol due to the delay in lymphodepletion and/or infusion, it will not be considered as a protocol deviation. If the intervals between the apheresis and the time of infusion exceed the intervals as specified in the protocol due to the manufacturing issues, it will not be considered as a protocol deviation.
2. Within 1 day prior to apheresis, the results of all tests at the apheresis visit should be assessed.
3. Baseline assessment (pre-lymphodepletion assessment) should be performed within 7 days prior to the lymphodepletion, except that the vital signs and physical examination should be performed within 1 day prior to the lymphodepletion. Pre-lymphodepletion assessment requires that the subject has not achieved a complete response (CR), this assessment may be confirmed by local laboratory results, but central laboratory results which are considered as baselines should be completed at the same time.

Baseline tumor burden assessment within 14 days prior to the start of lymphodepletion are acceptable, except for the bone marrow aspiration/biopsy-related assessments

within 4 weeks are acceptable. Prior to lymphodepletion, the appropriate tests should be repeated to confirm that subjects meet the criteria for lymphodepletion.

4. Subjects must be re-evaluated by the investigator prior to cell infusion and only those subjects who meet the criteria for cell infusion may be infused. If the subject does not meet the criteria for cell infusion, the infusion can be delayed for up to 2 weeks. If the delay exceeds 2 weeks, the investigator will evaluate whether the subject should have repeat pre-lymphodepletion assessment and lymphodepletion. Subjects will be hospitalized for at least 14 days after infusion, and the hospitalization for the days 15-28 will be based on requirement and institutional guideline. Prolonged hospitalization due to institutional guideline will not be recorded as an SAE.
5. The primary follow-up period is from 1 day after cell infusion to 2 years after cell infusion. After 3 months of cell infusion, follow-up will be every 3 months until disease progression, withdrawal of consent, death, loss to follow-up, or termination of the study by the sponsor, whichever occurs first.
6. The long-term follow-up period includes a long-term follow-up period and a post-dropout follow-up period.

Long-term Follow-Up Period: Subjects who complete the primary follow-up period of 2 years after cell infusion without disease progression will be followed for long-term follow-up every 6 months (180 days $\pm$ 28 days) until disease progression, withdrawal of consent, loss to follow-up, death, or 15 years after cell infusion, whichever occurs first (refer to 5.8.1 Long-term follow-up).

Post-dropout follow-up: Subjects who have completed a dropout visit will be followed up every 6 months from the date of the last visit until 5 years after the cell infusion. Subjects who have completed a dropout visit will be followed up by telephone or questionnaire every 6 months from 5 to 15 years after cell infusion and every 12 months at the study site (refer to 5.8.2 Post-dropout follow-up).

7. Dropout/End of study: Dropout refers to the situation where a subject in the study no longer undergoes efficacy evaluation due to disease progression, starting a new anti-myeloma treatment or other reasons. The subject will receive a dropout visit and undergo the follow-up as specified in this protocol. If a new anti-myeloma therapy has been started prior to the dropout visit, unless the subject withdraws the ICF, all items of the dropout visit should be completed within the time window as far as possible, with detailed chronological documentation of the external diagnostic basis for disease progression and the course of anti-myeloma therapy. The efficacy assessment should not be repeated within 4 weeks of the last confirmed efficacy assessment at two consecutive visits; other tests should not be repeated within 1 week of the last test; and the RCL test at the dropout visit should not be repeated within 1 year of the last test after infusion.

End of study (EOS) refers to the situation where a subject withdraws from the study due to CT103A cell manufacturing failure, failure to receive CT103A infusion, withdrawal of informed consent, death, loss to follow-up, study termination by the sponsor or other reasons (except for disease progression or starting a new anti-tumor

treatment). Except for death and loss to follow-up, an EOS visit should be performed whenever possible. Subjects who have not received the cell infusion are not required to undergo an EOS visit. The tests at the EOS visit does not need to be repeated within 1 week of the last test; the RCL test at the EOS visit does not need to be repeated within 1 year of the last test after the cell infusion.

8. Subjects must meet all inclusion criteria and none of the exclusion criteria during the screening period to be enrolled.
9. Subjects with a history of previous surgery or non-oncologic chronic disease that has resolved or recovered to a state of no clinical significance during the screening period will be recorded as a medical history.
10. Any abnormal symptoms, signs, abnormal laboratory or ancillary test results associated with a non-study medical condition that remain clinically significant during the screening period or are found between the signing of the ICF and enrollment will be recorded as a concomitant medical condition. Abnormal test results during the screening period that are caused by the study procedure will be recorded as AE.
11. All medications (including nutritional supplements such as vitamins, solvents, or solvents with therapeutic effects) and non-drug treatments used within 30 days prior to signing the informed consent should be recorded.
12. Imaging-based assessment: Low-dose whole-body CT or PET-CT can be performed for skeletal survey during the screening period, if low-dose whole-body CT or PET-CT is not available, local CT/MRI can be performed instead. In addition to the examination during the screening period, the imaging-based assessments at other visits should be done if extramedullary disease (EMD) is present prior to cell infusion or as determined by the investigator based on the clinical indications of the subjects (e.g., suspected achievement of CR or disease progression). The examination method for each part of the same subject during the follow-up period should be consistent. For subjects who have a mass as detected by CT or MRI that is inconsistent with the investigator's assessment, PET-CT may be added to assess the tumor activity. Imaging examination results within 4 weeks prior to ICF signing are acceptable.
13. Weight will be measured within 1 day before apheresis and in the pre-infusion assessment; height and weight will be remeasured before the lymphodepleting chemotherapy, based on which the body surface area is calculated. Body surface area calculation formula: $\text{body surface area} = \text{SQRT}(\text{height cm} \times \text{weight kg}/3600)$.
14. On the day of CT103A cell infusion, vital signs (temperature, respiratory rate, heart rate, blood pressure) should be measured at 15 ± 3 minutes before the start of cell infusion, at the start of cell infusion and within 1 hour (every 15 ± 3 minutes) after cell infusion. First aid facilities should be available during cell infusion for timely treatment of severe allergic reactions, severe hypotension, or other reactions. Body temperature should be measured twice daily (at least 6 hours between measurements)

until D28 and, if the temperature is abnormal, closely monitored until it is normal. If the subject is discharged during this period, a thermometer should be issued to record the temperature daily and recorded on the patient record card.

15. Physical examination should include at least the following: skin, mucous membranes, lymph nodes, head, neck, chest, abdomen, spine/extremities, and nervous system.
16. On the day of CT103A cell infusion, a 12-lead electrocardiogram will be performed 1 hour ($\pm$ 10 minutes) after the start of cell infusion. A bedside 12-lead ECG will be performed at any time if signs of abnormal cardiac function, such as panic, shortness of breath, and chest pain, occur. During the treatment and follow-up period, the investigator may decide to perform an additional electrocardiogram or echocardiogram depending on the patient's symptoms and signs suggesting abnormal heart function.
17. Oxygen saturation is measured by pulse oximetry and at least twice daily during CRS (at least 6 hours between measurements).
18. For women of childbearing potential only. Pregnancy test should be performed at dropout visit if the dropout visit is completed within 2 years of CAR-T cell infusion. Women of non-childbearing potential are defined as: 1. Menopausal women (absence of menstruation for at least 1 year); 2. Women with bilateral ovariectomy or hysterectomy.
19. Virologic/syphilis tests include: Hepatitis B test, HCV antibody, HIV antibody, EBV DNA (test results will not be used as the basis for inclusion in this study), CMV DNA and syphilis; virologic/syphilis test results within 4 weeks prior to ICF signing are acceptable.
20. Hematology: red blood cell count, hemoglobin level, red blood cell specific volume, white blood cell count, platelet count, white blood cell classification (including the ratio and absolute count of neutrophils/eosinophils/basophils, lymphocytes/monocytes). Hematology will be performed on the day of infusion according to clinical needs.
21. Blood biochemistry should be performed in the fasting state and should include the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ -GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP or ALP), glucose (Glu), total protein (TP), albumin (ALB), globulin (G), albumin/globulin ratio (A/G), lactate dehydrogenase (LDH), urea/urea nitrogen (Urea/BUN), creatinine (CRE), uric acid (URIC), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), troponin, sodium (Na), potassium (K), magnesium (Mg), chloride (Cl), phosphorus (P). If creatine kinase (CK) and creatine kinase isoenzyme (CK-MB) are not included in the blood biochemistry tests, they will need to be tested separately.
22. The parameters of coagulation include prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin time (TT), fibrinogen (FIB), D-dimer and international normalized ratio (INR).
23. The parameters of urinalysis include urine leukocytes, urine protein, urine erythrocytes, urine glucose. If urine protein $\geq$ + and considered unrelated to the study disease,

urine sediment microscopy should be performed, including red blood cell count, white blood cell count, epithelial cells, and bacteria.

24. Inflammatory factors include IL-6, C-reactive protein (CRP), and ferritin.
25. This test may not be performed at follow-up visit if non-secretory multiple myeloma is confirmed at screening and baseline (except for serum calcium and albumin-corrected calcium and β 2-microglobulin).
26. Bone marrow assessment results within 2 weeks prior to the screening and baseline visits will be acceptable (provided that the test items meet the study requirements, and a new sample should be collected if any item is missed). Bone marrow assessment is required within 7 days prior to lymphodepletion.

Bone marrow immunohistochemistry is recommended to include but are not limited to BCMA (for the first analysis), CD19, CD20, CD38, CD56, CD138, κ light chain, and λ light chain.

Cytogenetic abnormality was assessed by the FISH method (CD138+ magnetic bead sorting of myeloma cells or concurrent cytoplasmic immunoglobulin staining was recommended to differentiate plasma cells). Suggested loci for detection include but are not limited to IgH translocation, 17p- (p53 deletion), 13q14 deletion, 1q21 amplification, and if FISH is positive for IgH translocation, further testing is recommended for t(4;14), t(11;14), t(14;16), and t(14;20). Cytogenetic testing is only required in the screening period. If the screening test fails or is not detected, it can be repeated at the pre-lymphodepletion visit.

For bone marrow flow cytology, 8 or more antibody markers are recommended and are suggested to include but not limited to: BCMA, CD19, CD38, CD45, CD56, CD20, CD138, cytoplasmic κ light chain, and cytoplasmic λ light chain. Bone marrow immunohistochemistry or bone marrow flow cytology results are acceptable during the screening period.

Minimal residual disease (MRD) is detected using next-generation flow (NGF) methods. NGF testing is included in the bone marrow flow cytology examination. Bone marrow aspiration/biopsy is required at post-infusion follow-up visits if the subject has achieved $\geq$ VGPR or disease progression, and at other follow-up visits as deemed necessary by the investigator. However, for non-secretory subjects, these tests are required at all visits for efficacy assessment.

27. Venous blood will be collected for free BCMA testing according to the central laboratory manual.
28. Venous blood will be collected for immunogenicity testing, including human anti-CAR antibody testing, according to the central laboratory manual.
29. Venous blood will be collected for replication competent lentivirus testing (RCL) according to the central laboratory manual. The timepoints for RCL testing during the primary follow-up period are baseline examination, 90 days (time window $\pm$ 14 days), 180 days (time window $\pm$ 14 days), 360 days (time window $\pm$ 14 days), 720 days

(time window $\pm$ 14 days) after cell infusion until the dropout visit, and as needed if there is clinical evidence of suspected RCL. RCL testing should be performed if adverse events suspected to be related to RCL occur during the long-term follow-up period or post-dropout follow-up period, and follow-up up to 15 years is required for long-term surviving patients.

30. An additional 3 ml of blood may be collected at each PK blood collection time point to study the changes in cytokine or T cell subsets in vivo.
31. PK blood collection will be used for testing peripheral blood BCMA CAR-T cell and lentiviral vector copy number (VCN). The collection of PK samples is required at the same time of hematology. If hematologic tests are not done on the same day, results within 24 hours from the time of PK collection will be acceptable.
32. Venous blood is collected for VCN testing (using ddPCR assay) according to the central laboratory manual. The test was performed every 6 months ($\pm$ 28 days) at the 5-year post-cell infusion follow-up visits, regardless of whether the test value was below the lower limit of detection; the test was performed every 12 months at the 5 to 15-year post-cell infusion follow-up visits until study completion or early withdrawal from the study, or 2 consecutive tests below the lower limit of detection, whichever occurred first; if the last 2 VCN tests within 4-5 years post-cell infusion were below the lower limit of detection, the VCN test was not required at the 5 to 15-year post-cell infusion follow-up visit.
33. 3 ml of apheresis samples will be collected and used to study the effect of T cell subpopulations on the survival of CT103A in vivo.
34. Lentiviral genomic insertion site assays were performed to assess lentiviral genomic insertion site events. The frequency of testing during the long-term follow-up period or post-dropout follow-up period is synchronized with VCN testing, and testing is not required when the VCN test value is below the lower limit of detection.
35. Medications to prevent infusion reactions are allowed prior to CAR-T cell infusion, such as acetaminophen, promethazine, diphenhydramine hydrochloride, and calcium gluconate.
36. According to the IMWG 2016 criteria, documentation of response requires two consecutive measurements of the applicable disease parameter (serum M-protein, urine M-protein, or serum FLC), performed at any time (no minimum interval is required, it can be done on the same day); however, to confirm response or progressive disease, two discrete samples are required; testing cannot be based on the splitting of a single sample. Bone marrow and imaging assessment do not need to be confirmed by two assessments. Response assessment will continue beyond relapse from complete response (CR) until disease progression is confirmed.
37. Adverse events (AEs) will be recorded from the time of ICF signing. The results during the screening period will not be recorded as AEs, unless caused by study procedures. AEs will be collected until 2 years after CT103A cell infusion (if PFS $\geq$ 24 months) or dropout visit (24 months > PFS $\geq$ 6 months). If the dropout occurs within 6 months

after CT103A cell infusion, efforts should be made to collect AEs up to 6 months after the cell infusion provided that the subject cooperates with the collection. Subjects entering the long-term follow-up period or post-dropout follow-up period are required to collect CT103A related adverse events that occur in the follow-up period.

38. All serious adverse events (SAEs) occurring from the time of ICF signing should be reported. Subjects entering the long-term follow-up period or post-dropout follow-up period are required to collect SAEs that related to the investigational product (IP). In addition, SAEs for malignancy, neurologic, immunogenic or autoimmune type diseases, and infections occurring within 5 years post-infusion need to be collected for follow-up regardless of whether they are related to the IP.
39. Medications (including nutritional supplements such as vitamins, therapeutically active lysates or solvents) and non-drug treatments administered from the time of ICF signing will be recorded as concomitant treatments. The collection of concomitant treatments starts from the ICF signing until 2 years after CT103A cell infusion (if PFS $\geq$ 24 months) or until the drop-out/withdrawal visit (24 months > PFS $\geq$ 6 months), whichever occurs first. If the disease progression occurs within 6 months after CT103A cell infusion, efforts should be made for the collection until 6 months after the cell infusion. Subjects who have entered the long-term follow-up period are required to be followed for subsequent concomitant treatments of CT103A-related AEs/SAEs. All concomitant medications (including permitted and prohibited concomitant medications) and treatments should be recorded.
40. After apheresis and before lymphodepletion, bridging therapy may be used to maintain disease stability at the discretion of the investigator, and the decision to use bridging therapy will be made with the approval of the sponsor. Bridging therapy must be a short-term treatment previously received by the subject and should not be an anti-CD38 monoclonal antibody. Pre-lymphodepletion assessments will be performed at least 7 days after bridging therapy. Lymphodepleting chemotherapy is not allowed in subjects who have achieved CR or better according to IMWG (2016) criteria after bridging therapy.
41. Subsequent anti-myeloma treatment includes drug/non-drug treatments related to the study disease, such as radiotherapy, chemotherapy, hematopoietic stem cell transplantation (HSCT) therapy, gene therapy, surgery, and any other anti-tumor treatment, with gene therapy to be clarified if viral vectors are used.

1. Introduction

1.1 Disease Background

Multiple myeloma (MM), the second most common hematologic malignancy, occurs predominantly in the elderly¹. It is characterized by uncontrolled and progressive proliferation of plasma cells that undergo clonal expansion. The disease reduces the patient's resistance to infection, causes serious bone deformity (with bone pain, pathologic fractures, and hypercalcemia), anemia, renal failure, neurologic complications and hyperviscosity syndrome, and the progression of the disease eventually leads to death.

Multiple myeloma has a high morbidity and mortality rate, accounting for approximately 1% of all malignancies and 13% of blood cancers. The American Cancer Society's "Cancer Statistics 2018" annual report published in "CA: A Cancer Journal for Clinicians" estimates that the number of new cancer cases in the United States in 2018 was 1,735,350 (856,370 for men and 878,980 for women); the number of cancer deaths was 609,640 (323,630 for men and 286,010 for women); the number of new cases of myeloma was 30,770 and the number of deaths was 12,770, accounting for 18% of hematologic malignancies and 2% of malignant deaths². At least 60,000 new cases of multiple myeloma are diagnosed each year in China, with most patients surviving for only 3-5 years.

1.1.1 Treatment options for multiple myeloma

Treatment options for multiple myeloma depend on the age, performance status, comorbidity, disease aggressiveness and related prognostic factors. The treatment of multiple myeloma has changed markedly over the past 10 years with the introduction of novel immunomodulators thalidomide, lenalidomide, the first-generation proteasome inhibitor (PI) Velcade® (bortezomib), and anti-CD38 monoclonal antibodies (daratumumab and isatuximab). Several randomized, controlled clinical studies have shown that integrating novel treatments has significantly increased the response rate and improved the progression-free survival (PFS) and overall survival (OS)³. Additionally, two CAR-T therapies, idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti), have been approved by the FDA as salvage therapy for patients with relapsed/refractory multiple myeloma (RRMM). These drugs represent the novel approach of targeted immunotherapy, which use the body's own immune system to specifically kill cancer cells. Overall, advances in the treatment of multiple myeloma have significantly improved patient outcomes. However, due to residual myeloma stem cells, changes in the cellular microenvironment, activation of anti-apoptotic pathways, expression of resistance genes or clonal evolution, the vast majority of patients still eventually face disease relapse or progression^{4,5}. RRMM has a low response rate and a short median survival, which significantly impacts the health of these patients.

Currently, patients with RRMM have the following treatment options according to the "Guidelines for the diagnosis and management of multiple myeloma in China (2022

revision) ":

- Participation in a clinical trial is recommended;
- First relapse: Combination therapy with 3-4 drugs such as dexamethasone, proteasome inhibitors (carfilzomib, ixazomib, bortezomib), immunomodulatory agents (pomalidomide, lenalidomide), daratumumab, and exportin-1 inhibitors (selinexor);
- Multiple relapses: Combination therapy with 2-4 drugs such as dexamethasone, proteasome inhibitors, immunomodulatory agents, daratumumab, XPO-1 inhibitors, and cytotoxic drugs, e.g., DCEP ± V (dexamethasone/ cyclophosphamide/ etoposide/ cisplatin ± bortezomib), DT-PACE ± V regimen (dexamethasone/ thalidomide/ cisplatin/ doxorubicin/ cyclophosphamide/ etoposide ± bortezomib) (where lenalidomide may be used instead of thalidomide);
- Autologous or allogeneic hematopoietic stem cell transplantation

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Multiple Myeloma (2022 V1) published in the United States, the standard treatment options for RRMM are as follows:

- For patients with RRMM, it is recommended to continue previous treatment options, participate in clinical trials, and receive autologous or allogeneic stem cell transplantation;
- For patients with disease progression after allogeneic hematopoietic stem cell transplantation, it is recommended to continue previous treatment options, participate in clinical trials, and receive donor lymphocyte infusion (DLI);
- For patients with disease progression after autologous hematopoietic stem cell transplantation, it is recommended to continue previous treatment options, participate in clinical trials, and receive allogeneic hematopoietic stem cell transplantation;

The selection of appropriate treatment options for RRMM patients remains a major challenge. According to the recommended guidelines, clinical trials are prioritized for relapsed/refractory multiple myeloma.

In recent years, several clinical research institutions and biotechnology companies have conducted clinical trials of CAR-T cells with different targets for the treatment of RRMM. To date, several clinical trials of BCMA CAR-T cells (engineered with different CARs) have revealed the clinical study data involving more than 200 evaluable patients with relapsed/refractory disease^{6,7,8,9,10,11}. These data show that the response rate ranges from 60% to 100% and even complete responses with negative minimal residual disease (MRD) are achieved with an effective dose after treatment. In the two recent studies, most patients had no progression, with a median follow-up of 6-10 months, and some patients had sustained response for more than a year. Toxicity is similar to CD19 CAR-T cells, including cytokine release syndrome and reversible severe neurotoxicity.

1.1.2 CT103A

The investigational product (IP) is a fully human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A).

CT103A is an individualized tailored, BCMA-targeted, genetically engineered autologous T cell immunotherapy product that identifies and eliminates BCMA-expressing malignant and normal cells. CAR specifically recognizes BCMA with a low-immunogenic fully human single chain fragment variable (ScFv), promotes CAR-T activation, proliferation, cytokine secretion and target cell killing through the CD3 ζ domain, and enhances CAR-T proliferation and persistence through co-stimulatory signaling via 4-1BB.

CT103A cells have high affinity for BCMA antigens and efficiently kill antigen-loaded cells in vitro and in vivo preclinical studies. Clinical studies of CT103A in China have demonstrated favorable safety and robust efficacy in the treatment of RRMM.

Comprehensive non-clinical and clinical information of CT103A is available in the Investigator's Brochure (IB). The reference safety information of CT103A is included and adverse drug reactions that may be related to CT103A are listed in the IB.

1.2 Summary of Non-clinical Findings

To characterize the biological activity and mechanism of action of CT103A, the following preclinical studies were performed:

- In vitro pharmacology: identification of scFv, binding affinity and specificity of CT103A to the recombinant human BCMA Fc protein; degranulation activity in the presence or absence of BCMA; ability to produce cytokines; antigen-dependent CT103A expansion; cytotoxicity against BCMA+ multiple myeloma cells.
- In vivo pharmacology: The anti-tumor efficacy of CT103A was evaluated in immunodeficient female M-NSG mice.
- Pharmacokinetic/Biodistribution Studies.
- General in vivo toxicology studies.

1.3 Summary of Clinical Findings

1.3.1 XL-LCYJ-0003 study

The XL-LCYJ-0003 study is an investigator-initiated, single-center, dose-escalating, single-arm, open-label, standard "3+3" designed clinical trial. It consists of two phases: dose escalation (n = 12) and dose expansion (n = 11). The study evaluated the tolerability, safety, and efficacy of CT103A in patients with relapsed/refractory plasma cell tumors and clarified the expansion and persistence of CT103A in vivo. Taken together, the results of these studies established the RP2D.

As of June 30, 2021, the study had screened 37 RRMM patients at one study site and 23 (5 in the 0.5×10^6 CAR-T cells/kg group, 9 in the 1.0×10^6 CAR-T cells/kg group, 6 in the 3.0×10^6 CAR-T cells/kg group and 3 in the 6.0×10^6 CAR-T cells/kg group) completed cell infusion. Of the 23 subjects who received cell infusion, 7 subjects

completed the primary follow-up period, 3 subjects were in the primary follow-up period, and 13 subjects withdrew from the hospitalization period or the primary follow-up period due to disease progression (n = 7), death (n = 3), adverse event (n = 1), protocol deviation (n = 1) and ICF withdrawal (n = 1). The best ORR at 3 months was 100% (95% CI: 85.2%, 100%) for all 23 subjects receiving CT103A infusion, with 73.9% (95% CI: 51.6%, 89.8%) achieving $\geq$ VGPR and 52.2% (95%CI: 30.6%, 73.2%) achieving CR/sCR. The best ORR at 6 months was 100% (95% CI: 85.2%, 100%), with 82.6% (95% CI: 61.2%, 95.1%) achieving $\geq$ VGPR and 65.2% (95% CI: 42.7%, 83.6%) achieving CR/sCR. After 6 months post-infusion, 7 (77.8%) subjects in the 1.0×10^6 CAR T cells/kg dose group achieved VGPR or better.

In terms of safety, subjects, only one subject in the 6.0×10^6 CAR-T cells/kg group experienced grade 4 CRS (determined as dose-limiting toxicity [DLT]). All 23 subjects who received cell infusion experienced treatment-related adverse events (TRAEs) and grade 3 or higher TRAEs. Grade 3 or higher TRAEs were mainly related to hematologic toxicity, cytokine release syndrome (CRS), metabolic and nutritional disorders, liver abnormalities and coagulation abnormalities. Grade ≥ 3 TRAEs with an incidence of $\geq 10\%$ included decreased white blood cell count (65.2%), decreased lymphocyte count (60.9%), decreased neutrophil count (60.9%), decreased platelet count (43.5%), anemia (43.5%), CRS (21.7%), fever (21.7%), elevated aspartate aminotransferase (17.4%), and decreased fibrinogen (13.0%). There were no TRAEs leading to discontinuation, withdrawal from the study, or death.

DLT

Only one DLT with grade 4 CRS was observed in the 6.0×10^6 CAR-T cells/kg dose group, and this subject died out of hospital due to respiratory failure caused by severe pulmonary infection and sepsis. Testing of the patient's samples revealed a mutation in the PSENEN gene, resulting in abnormally high expression of BCMA on the plasma cells. After discussions between the investigators and sponsors, it was decided to stop the dose escalation study and to explore a lower dose of 0.5×10^6 CAR-T cells/kg and to expand the dose level of 1.0×10^6 CAR-T cells/kg to 6 subjects to further confirm the safety and preliminary efficacy.

CRS and ICNAS

Almost all subjects (95.7%) experienced CRS after CT103A infusion, and the severity of CRS showed some correlation with the dose of CT103A. No grade 3 or higher CRS was observed in the 0.5×10^6 CAR-T cells/kg dose level, grade 3 CRS was observed in 2 of 9 subjects (22.2%) in the 1.0×10^6 CAR-T cells/kg dose level, and 2 of 3 subjects (66.7%) in the 6.0×10^6 CAR-T cells/kg dose group, with 1 case (33.3%) of grade 4 CRS.

As of June 30, 2021, no subjects had experienced immune effector cell-associated neurotoxicity syndrome (ICANS).

Other common adverse events

In addition to CRS, other common TRAEs include hematologic toxicity, CRS, metabolic

and nutritional disorders, gastrointestinal reactions, abnormal coagulation, hyperglobulinemia, abnormal liver function and abnormal cardiac function. Most TRAEs resolved within 3 months and the incidence did not correlate significantly with dose.

Serious Adverse Events

15 subjects (65.2%) experienced SAEs, all of which occurred after cell infusion. the most common SAEs were infectious and invasive diseases and laboratory abnormalities. SAEs with an incidence of $\geq 5\%$ included infectious pneumonia (21.7%), decreased platelet count (21.7%), herpes zoster (8.7%), infectious shock, and decreased neutrophil count (8.7%). Two (8.7%) subjects had treatment-related SAEs, one subject (0.5×10^6 CAR T cells/kg group) had a grade 4 thrombocytopenia, and one subject (6.0×10^6 CAR T cells/kg group) had a grade 4 CRS.

Deaths

A total of 8 subjects died by June 30, 2021. Of these, 5 subjects died due to adverse events that were unrelated or possibly unrelated to the IP (4 subjects died due to AEs that occurred during the study; the other subject died due to an AE that occurred after study discontinuation, was judged by the investigator to be unrelated to the IP, and was not recorded in the EDC according to the AE recording rules in the study protocol), 2 subjects died of unknown reasons after dropout due to disease progression; in one case, after the subject withdrew the ICF, the subject's family informed that the subject had a disease progression in January 2021 and died on February 19, 2021 with unknown details. There were no TRAEs that led to death.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

As of June 30, 2021, the PK and PD data from the XL-LCYJ-0003 study showed that:

The median vector copy number (VCN) C_{max} for the 1.0×10^6 CAR-T cells/kg, 3.0×10^6 CAR-T cells/kg, 6.0×10^6 CAR-T cells/kg groups in dose-escalation phase and the 0.5×10^6 CAR-T cells/kg and 1.0×10^6 CAR-T cells/kg groups in the dose-expansion phase were 91250 (56500, 112000) copies/ug DNA, 48459.50 (10725, 132500) copies/ug DNA, 101000 (62000, 195522) copies/ug DNA, 26300 (589, 116461) copies/ug DNA, and 98000 (10800, 167500) copies/ug DNA. The median T_{max} ranged from 10 to 16 days. The median C_{max} , T_{max} , AUC_{0-28d} and AUC_{0-90d} of VCN did not show a significant difference with increasing dose during the dose-escalation phase. In the dose-expansion phase, C_{max} , AUC_{0-28d} and AUC_{0-90d} were higher in the 1.0×10^6 CAR-T cells/kg group than in the 0.5×10^6 CAR-T cells/kg group. VCN were still detectable in three of the seven subjects at the two-year follow-up. Two subjects were in the 1.0×10^6 CAR-T cells/kg dose group and one subject was in the 3.0×10^6 CAR-T cells/kg dose group.

In the dose-escalation phase, the concentration of BCMA CAR-T cells could not be calculated due to missing values. In the dose-expansion phase, median cell concentrations in the 0.5×10^6 CAR-T cells/kg and 1.0×10^6 CAR-T cells/kg dose groups peaked at D30 and D17 at 1.51×10^8 cells/L and 1.66×10^9 cells/L, respectively.

The median CAR-T cell concentration in the 1.0×10^6 CAR-T cells/kg dose group was 11 times higher than that in the 0.5×10^6 CAR-T cells/kg dose group. The cell concentrations in both dose groups decreased slowly after reaching the peak.

Free BCMA in peripheral blood decreased rapidly after cell infusion in all dose groups. One month after cell infusion, free BCMA decreased to a level below the lower limit of quantitation (LLOQ, 3.2 ng/mL) in most subjects, and this level was maintained for up to 25 months after cell infusion. There was no significant correlation between the lowest level of free BCMA and dose.

Free BCMA levels in peripheral blood after infusion was strongly correlated with disease status. Two subjects showed a significant rebound in free BCMA with disease progression. Subjects in sustained response had free BCMA consistently below the LLOQ or maintained at lower levels.

1.3.2 Selection for Phase II Recommended Dose (RP2D)

CT103A is safe and effective in clinical application with good proliferation and persistence. The clinical efficacy, the proliferation level, and persistence in the body might not improve with increased dose, indicating that the clinical benefit was not dose dependent. Better safety and PK characteristics were observed in the 1.0×10^6 CAR-T cells/kg group. Considering these results and the rate of successful production of CAR-T cells, 1.0×10^6 CAR-T cells/kg was selected as the RP2D.

2. Objectives and Endpoints

2.1 Objectives

2.1.1 Phase I

Primary objectives:

- To evaluate the safety of CT103A at the recommended phase II dose (RP2D)

Secondary objectives:

- To evaluate the efficacy of CT103A in the treatment of patients with RRMM
- To evaluate the pharmacokinetic (PK) characteristics of CT103A
- To evaluate the pharmacodynamic (PD) characteristics of CT103A

Exploratory objectives:

- To evaluate the immunogenicity of CT103A
- To monitor the generation of replication competent lentivirus (RCL)

2.1.2 Phase II

Primary objectives:

- To evaluate the efficacy of CT103A in the treatment of patients with RRMM

Secondary objectives:

- To evaluate the safety of CT103A in the treatment of patients with RRMM
- To evaluate the pharmacokinetic (PK) characteristics of CT103A
- To evaluate the pharmacodynamic (PD) characteristics of CT103A

Exploratory objectives:

- To evaluate the immunogenicity of CT103A
- To monitor the generation of replication competent lentivirus (RCL)

2.2 Endpoints

2.2.1 Phase I

Primary endpoints:

- Safety endpoints:
 - Incidence and severity of adverse events (per NCI-CTCAE v5.0);
 - Incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (per ASTCT 2019 criteria);
 - Changes in laboratory test results;
 - Vital signs and physical examination.

Secondary endpoints:

- Efficacy endpoints (IMWG criteria):
 - Overall response rate (ORR) at 3 months assessed by the independent review committee (IRC) and the investigator: the proportion of subjects who achieve PR or better at 3 months as defined by the International Myeloma Working Group (IMWG) response criteria;
 - Best ORR as assessed by the IRC and the investigator: the proportion of subjects who achieve PR or better as defined by the IMWG response criteria;
 - Progression-free survival (PFS) as assessed by the IRC and the investigator: Duration from the date of CT103A infusion to the date of first documented evidence of progressive disease or death due to any cause;
 - Overall survival (OS): Duration from the start of CT103A treatment to the subject's death (due to any cause);
 - Duration of response (DOR) as assessed by the IRC and the investigator: Duration from the date of the first documented response (PR or better) to the date of the first documented evidence of progressive disease, as defined by the IMWG criteria;
 - Time to response (TTR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of the first documented response (PR or better);
 - Time to complete response (TTCR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of first documentation of a complete response (CR) or stringent complete response (sCR);
 - MRD response assessment: The proportion of subjects achieving MRD-negativity and the duration of MRD-negativity.
- Pharmacokinetics (PK): The maximum concentration ($C_{\max}$) of BCMA CAR-T cells and lentiviral vector copy number (VCN) of CT103A in peripheral blood after CT103A infusion; time to reach $C_{\max}$ ($T_{\max}$); area under the curve (AUC) from 0 to 28 days (AUC_{0-28d}), AUC from 0 to 90 days (AUC_{0-90d}), AUC from 0 to 180 days (AUC_{0-180d}), and AUC from 0 to the last quantifiable time point;
- Pharmacodynamics (PD): circulating soluble BCMA (sBCMA) in peripheral blood; cytokine and immune-related protein including CRP, IL-6 and ferritin in peripheral blood.

Exploratory endpoints:

- Immunogenicity: presence of human anti-CAR antibodies, and titer of confirmed positive antibodies in peripheral blood;

- Presence of replication competent lentivirus (RCL) in peripheral blood.

2.2.2 Phase II

Primary endpoints:

- ORR at 3 months as assessed by the IRC: The proportion of subjects who achieved PR or better at 3 months as defined by the IMWG response criteria.

Secondary endpoints:

- Efficacy endpoints (IMWG criteria):
 - ORR at 3 months as assessed by the investigators: the proportion of subjects who achieved PR or better at 3 months as defined by the IMWG response criteria;
 - Best ORR assessed by the IRC and the investigator: the proportion of subjects who achieved PR or better as defined by the IMWG response criteria;
 - Progression-free survival (PFS) as assessed by the IRC and the investigator: Duration from the date of CT103A infusion to the date of first documented evidence of progressive disease or death due to any cause;
 - Overall survival (OS): Duration from the start of CT103A treatment to the subject's death (due to any cause);
 - Duration of response (DOR) assessed by the IRC and the investigator: Duration from the date of the first documented response (PR or better) to the date of first documented evidence of progressive disease, as defined by the IMWG criteria;
 - Time to response (TTR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of the first documented response (PR or better);
 - Time to complete response (TTCR) assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of first documentation of a complete response (CR) or stringent complete response (sCR);
 - MRD response assessment: The proportion of subjects achieving MRD-negativity and the duration of MRD-negativity.
- Safety endpoints:
 - Incidence and severity of adverse events (per NCI-CTCAE v5.0);
 - Incidence and severity of CRS and ICANS (per ASTCT 2019 criteria);
 - Changes in laboratory test results;
 - Vital signs and physical examination.

- Pharmacokinetics (PK): The maximum concentration ($C_{\max}$) of BCMA CAR-T cells and lentiviral vector copy number (VCN) of CT103A in peripheral blood after CT103A infusion; time to reach $C_{\max}$ ($T_{\max}$); area under the curve (AUC) from 0 to 28 days (AUC_{0-28d}), AUC from 0 to 90 days (AUC_{0-90d}), AUC from 0 to 180 days (AUC_{0-180d}), and AUC from 0 to the last quantifiable time point;
- Pharmacodynamics (PD): circulating soluble BCMA (sBCMA) in peripheral blood; cytokine and immune-related protein including CRP, IL-6 and ferritin in peripheral blood.

Exploratory endpoints:

- Immunogenicity: presence of human anti-CAR antibodies, and titer of confirmed positive antibodies in peripheral blood;
- Presence of replication competent lentivirus (RCL) in peripheral blood.

3. Study Design

3.1 Overview of Study Design

This study was designed in accordance with the requirements of the Chinese Good Clinical Practice (GCP) and the "Technical Guidelines for the Research and Evaluation of Cell Therapy Products" and other regulatory guidelines, and was optimized based on the "Considerations for the Design of Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy for Malignant Tumors of the Hematopoietic System" and "Technical Guidelines for Conditional Approval of Drugs (Trial)" issued by the Clinical Department of the Center for Drug Evaluation (CDE) for biological products.

In an investigator-initiated, non-registered clinical trial of CT103A using a "3+3" dose escalation design for the treatment of RRMM patients (see Section 1.3 for details), a total of 12 subjects were enrolled and received three dose levels of CT103A injection, including 1.0×10^6 CAR-T cells/kg ($n = 3$), 3.0×10^6 CAR-T cells/kg ($n = 3$), and 6.0×10^6 CAR-T cells/kg ($n = 3$). No dose-limiting toxicity (DLT) was observed in the 1.0×10^6 and 3.0×10^6 CAR-T cells/kg dose groups. Only one case of DLT was observed in the 6.0×10^6 CAR-T cells/kg dose group, which was grade 4 CRS. Through further expansion studies of 11 subjects who received 1.0×10^6 CAR-T cells/kg ($n = 6$) and lower doses of 0.5×10^6 CAR-T cells/kg ($n = 5$), the safety, efficacy, PK, and PD of the dose escalation and expansion phases were comprehensively analyzed and 1.0×10^6 CAR-T cells/kg was identified as the recommended phase II dose (RP2D) for CT103A.

In this study, a dose-expansion (phase I) study was first planned to further evaluate the safety and efficacy of CT103A injection at the RP2D dose level in patients with RRMM. Then, based on the preliminary results of the dose-expansion phase (phase I), the investigator and sponsor will communicate with the CDE to conduct a pivotal phase II clinical study to fully evaluate the efficacy and safety of CT103A injection at the RP2D dose. During the phase II study, the sponsor communicated with the CDE prior to submitting a conditional marketing application, as the manufacturing site will change after marketing. The CDE required that a bridging study should be conducted during the phase II study to confirm the clinical efficacy and safety of the investigational product after the change in manufacturing sites.

Overview of the Phase I Study Design

The Phase I study is a multi-center, open-label, dose-expansion study designed to evaluate the safety, PK and PD characteristics, and immunogenicity of the IP at the RP2D level, and to preliminarily observe the efficacy of CT103A in a small number of subjects with RRMM to provide a basis for the Phase II study.

Seven sites were selected for the Phase I study. After signing the informed consent form (ICF), eligible subjects received CT103A at the dose of 1.0×10^6 CAR-T cells/kg. This study was designed to enroll 6-20 subjects, with a total of 20 subjects were actually enrolled and 17 subjects received CT103A.

After all subjects completed the 1-month post-infusion safety evaluation, the sponsor

communicated with the CDE based on the available safety, efficacy, and PK data, and conducted the Phase II study after the communication.

Overview of the Phase II Study Design

The Phase II study will continue to enroll eligible subjects at the RP2D dose level (1.0×10^6 CAR-T cells/kg) established in the Phase I study, to confirm the efficacy and safety of the RP2D dose in RRMM patients. This study plans to enroll at least 109 subjects at the RP2D dose level (including the 17 subjects who completed in Phase I, 78 subjects who completed in Phase II, and at least 14 subjects intended for the bridging study).

Subjects meeting the inclusion criteria but not the exclusion criteria will receive a single dose of CT103A at the recommended dose level (1.0×10^6 CAR-T cells/kg). The study plans to follow all subjects for safety and efficacy until disease progression, withdrawal of informed consent, withdrawal from the study, death, loss to follow-up, death, study completion, or 15 years after cell infusion, whichever occurs first. Subjects who drop out will continue to be followed until study completion.

Study procedure

The study includes screening and enrollment, apheresis, bridging therapy, baseline assessment (pre-lymphodepletion assessment), lymphodepleting chemotherapy, rest assessment, cell infusion, primary follow-up period, and long-term follow-up period.

For newly initiated sites, there should be at least 14 days between infusions of the first three subjects.

3.1.1 Sample size

Phase I study:

- The enrollment has been completed, and a total of 23 subjects have received cell infusion.

Phase II study:

- Confirmatory study: The hypothesis test is based on whether the ORR at 3 months is greater than 35% (i.e., $H_0: p \leq 0.35$ vs $H_1: p > 0.35$). Therefore, assuming the 3-month ORR is 60% in the full analysis set (FAS), with a one-sided $\alpha = 0.025$, at least 53 subjects in the FAS are required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis. In this stage, 78 subjects have received cell infusion;
- Bridging study: The hypothesis test is based on whether the ORR at 3 months is greater than 35% (i.e., $H_0: p \leq 0.35$ vs $H_1: p > 0.35$). Combined with the results of the confirmatory study, the 3-month ORR in the FAS is expected to be 80% with a one-sided $\alpha = 0.025$. Therefore, a minimum of 14 subjects in the FAS population is required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis;
- Therefore, at least 109 subjects are required to complete the CT103A infusion in this study. However, considering a 10% drop-out rate between enrollment and

infusion, it is expected that a total of 120 to 125 subjects meeting the inclusion criteria are expected to be enrolled.

3.1.2 Sites

This study is a multi-center clinical study. 7 study sites were selected in phase I and 14 sites in phase II.

3.1.3 Determining dosage and route of administration

3.1.3.1 Dosage and route of administration

Currently, the infusion route for CAR-T cell therapy in clinical studies is mainly peripheral venous infusion. Since CT103A is a suspension of live cells, a single intravenous injection is currently the best route of administration.

Due to the unique nature of CAR-T cell products, there are significant differences between animals and humans. According to the "Technical Principles for the Research and Evaluation of Cell Therapy Products (Trial)" issued by the NMPA, previous clinical experience (if available) may help to reasonably determine the clinical starting dose. Combined with the safety and efficacy data of CT103A in a dose-escalation IIT study, a dose of 1.0×10^6 CAR-T cells/kg is planned for the phase I clinical trial.

3.1.3.2 Lymphodepleting regimen

Enrolled patients should undergo lymphodepleting chemotherapy prior to cell infusion. Clinical experience with CAR-T cell therapy in leukemia patients has shown that reducing lymphocytes in the body prior to CAR-T cell infusion can increase CAR-T cell expansion, persistence, and release of inflammatory cytokines. In general, fludarabine and cyclophosphamide are used for lymphodepletion, but there are differences in drug dosage and administration time in different clinical studies.

Combining the physique of Chinese patients and the experience gained from the previous IIT clinical study, this study will perform the lymphodepleting chemotherapy within 2-7 days before infusion with cyclophosphamide 500mg/m²/d and fludarabine 30 mg/m²/d for 3 consecutive days. If the subject has renal impairment or other conditions that require adjustment of the dose of the lymphodepleting medication, the investigator may adjust the dose of lymphodepletion drugs after comprehensive assessment and confirmation with the sponsor.

3.1.4 Study duration

This study is divided into a primary follow-up period and a long-term follow-up period. The primary follow-up period is from 1 day after cell infusion to 2 years after cell infusion. The entire primary follow-up period of the study is expected to be 4-5 years.

If the subject completes the primary follow-up period or withdraws from the study early, the subject should undergo long-term follow-up for up to 15 years after cell infusion.

3.2 Study population

Subjects with RRMM, male or female, aged 18 to 70, who meet all inclusion criteria and

none of the exclusion criteria may be enrolled in the study.

3.2.1 Inclusion Criteria

1. Greater than or equal to 18 years of age and less than or equal to age 70.
2. Documented diagnosis of multiple myeloma according to the IMWG diagnostic criteria; have received at least 3 prior lines of therapy, including proteasome inhibitor (PI) and immunomodulatory-based (IMiD) chemotherapy; documented disease progression during or within 12 months of the last anti-myeloma treatment (the progression for subjects whose last line treatment was CAR-T therapy was not limited to 12 months post-treatment).
3. Positive BCMA expression on tumor cells by immunohistochemistry (IHC) or flow cytometry is required prior to enrollment.
4. Presence of measurable lesion at screening as determined by any of the following criteria:
 - The proportion of primitive or monoclonal plasma cells $\geq 5\%$ by bone marrow cytology, bone marrow biopsy immunohistochemistry, or flow cytometry;
 - Serum M protein level: IgG type M protein ≥ 10 g/L, or IgA, IgD, IgE, IgM type M protein ≥ 5 g/L;
 - Urine M protein level ≥ 200 mg/24h;
 - Light chain multiple myeloma without measurable lesions in serum or urine: Involved serum free light chain ≥ 100 mg/L and abnormal serum κ/λ free light chain ratio.
5. ECOG score of 0 or 1 (refer to [Appendix 1](#))
6. Expected survival time is greater than or equal to 12 weeks.
7. Subjects must have adequate organ function and meet all of the following laboratory values prior to enrollment:
 - Hematology: Absolute neutrophil count (ANC) $\geq 1 \times 10^9/\text{L}$ (supportive growth factor is permitted, but must be without supportive treatment within 7 days prior to laboratory testing); absolute lymphocyte count (ALC) $\geq 0.3 \times 10^9/\text{L}$; platelet count $\geq 50 \times 10^9/\text{L}$ (must be without supportive blood transfusion within 7 days prior to laboratory testing); hemoglobin ≥ 60 g/L (without red blood cell [RBC] transfusion within 7 days prior to laboratory testing; the use of recombinant human erythropoietin is permitted);
 - Liver function: Alanine transaminase (ALT) and aspartate transaminase (AST) $\leq 2.5 \times$ upper limit of normal (ULN); serum total bilirubin $\leq 1.5 \times$ ULN;
 - Renal function: Creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula ≥ 40 ml/min;
$$\text{CrCl} = (140 - \text{Age}) \times \text{Mass (kg)} \times [0.85 \text{ if female}] / 72 \times [\text{Serum Creatinine (mg/dL)}]$$

- Coagulation function: Fibrinogen ≥ 1.0 g/L, activated partial thromboplastin time (APTT) $\leq 1.5 \times \text{ULN}$, prothrombin time (PT) $\leq 1.5 \times \text{ULN}$;
 - Oxygen saturation $\geq 91\%$;
 - Left ventricular ejection fraction (LVEF) $\geq 50\%$.
8. Female subjects of childbearing potential or male subjects with a partner of childbearing potential agree to use effective contraception methods from ICF signing until one year after CAR-T cell infusion.
 9. The subject must personally sign an informed consent form approved by the ethics committee.

3.2.2 Exclusion Criteria

1. Subjects with graft-versus-host-disease (GVHD) or those requiring long-term use of immunosuppressants.
2. Received autologous hematopoietic stem cell transplantation (Auto-HSCT) within 12 weeks prior to apheresis, received twice Auto-HSCT, received prior allogeneic hematopoietic stem cell transplantation (Allo-HSCT).
3. There are not enough peripheral blood mononuclear cells available for CAR-T cell manufacturing.
4. Received prior anti-myeloma therapies as follows:
 - Treatment with monoclonal antibodies within 21 days prior to apheresis, or
 - Treatment with cytotoxic chemotherapy or proteasome inhibitor within 14 days prior to apheresis, or
 - Treatment with immunomodulator within 7 days prior to apheresis, or
 - Anti-myeloma therapies other than those described above within 14 days or at least 5 half-lives (whichever is longer) prior to apheresis.
5. Use of glucocorticoids (defined as prednisone or equivalent > 20 mg/day) at a therapeutic dose within 7 days prior to apheresis. Physiologic replacement, topical, and inhaled steroids are permitted, nevertheless.
6. Uncontrolled hypertension under medical therapy.
7. Severe heart disease: Including but not limited to unstable angina, myocardial infarction (within 6 months prior to screening), congestive cardiac failure (New York Heart Association [NYHA] classification grade $\geq$ III), severe arrhythmia.
8. Unstable systemic disease as judged by the investigator: Including but not limited to severe hepatic, renal, or metabolic disease requiring therapy.
9. Malignancies other than multiple myeloma within 5 years prior to screening, excluding adequately treated cervical carcinoma in situ, basal or squamous epithelial cell skin cancer, localized prostate cancer after radical surgery, ductal carcinoma in situ of the breast after radical surgery.

10. History of organ transplantation.
11. Suspected or confirmed central nervous system involvement.
12. Have extramedullary lesions (except for a single paramedullary extramedullary lesion with maximum transverse diameter ≤ 3 cm).
13. Plasma cell leukemia ($\geq 5\%$ plasma cells in peripheral blood).
14. Major surgery within 2 weeks prior to apheresis, or planned surgery within 2 weeks after CT103A infusion (subjects planning to receive surgery under local anesthesia are permitted to be enrolled in this study).
15. Treated with other investigational products within 1 month prior to signing the informed consent form (ICF).
16. Uncontrollable active infection (excluding CTCAE grade 2 urinary and respiratory tract infections) within 7 days prior to apheresis.
17. Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with detectable hepatitis B virus (HBV) DNA in peripheral blood; positive hepatitis C virus (HCV) antibody with positive HCV RNA in peripheral blood; positive human immunodeficiency virus (HIV) antibody; positive cytomegalovirus (CMV) DNA; positive syphilis test.
18. Pregnant or breastfeeding women;
19. Have psychiatric disorders, conscious disorders, or central nervous system diseases;
20. Non-hematologic toxicities from previous anti-myeloma therapy have not recovered to baseline or grade ≤ 1 (NCI-CTCAE v5.0, except for alopecia and grade 2 peripheral neuropathy).
21. Any condition for which, at the discretion of investigators, participation would not be in the best interest of the subject.

3.2.4 Criteria for apheresis

- (1) The following requirements must be met within 1 day prior to apheresis:
 - Hematology: Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$; absolute lymphocyte count (ALC) $\geq 0.3 \times 10^9/L$; platelet count $\geq 50 \times 10^9/L$; hemoglobin ≥ 60 g/L; must be without supportive treatment within 7 days prior to the above tests.
- (2) The following requirements must be met within 7 days prior to apheresis:
 - Coagulation function: Fibrinogen ≥ 1.0 g/L, activated partial thromboplastin time (APTT) $\leq 1.5 \times$ ULN, prothrombin time (PT) $\leq 1.5 \times$ ULN;
- (3) Not treated with systemic steroids (other than inhaled or topical use) within 14 days prior to apheresis;
- (4) The subject does not meet the exclusion criteria 2), 4), 14) and 16) as reconfirmed;

- (5) There are no other conditions that, at the discretion of investigators, make the subjects unsuitable for apheresis.

3.2.5 Criteria for lymphodepleting chemotherapy

Subjects must complete the pre-lymphodepletion assessment prior to initiation of lymphodepleting chemotherapy and meet the following criteria:

- (1) If a subject receives bridging therapy after apheresis, the bridging therapy must have been completed ≥ 7 days prior to the pre-lymphodepletion assessment without achieving a complete response (CR) as assessed by the investigator;
- (2) Absence of severe active infection as determined by the investigator ($<$ grade 2 genitourinary infections and upper respiratory tract infections are excluded);
- (3) Axillary body temperature should be $\leq 38^{\circ}\text{C}$ within 48 hours prior to lymphodepleting chemotherapy;
- (4) Subjects must meet the following requirements within 7 days prior to the lymphodepleting chemotherapy:
 - Oxygen saturation $> 91\%$;
 - Left ventricular ejection fraction (LVEF) $\geq 50\%$;
- (5) Peripheral plasma cell percentage $< 10\%$;
- (6) Lymphodepletion treatment may be administered after investigator assessment of hematology, hepatic and renal function, and coagulation;
- (7) There are no other conditions that, at the discretion of investigators, make the subjects unsuitable for apheresis.

3.2.5 Criteria for CT103A infusion

Subjects must meet the following criteria prior to CT103A infusion:

- (1) Absence of severe active infection as determined by the investigator ($<$ grade 2 genitourinary infections and upper respiratory tract infections are excluded);
- (2) Axillary body temperature should be $\leq 38^{\circ}\text{C}$ within 48 hours prior to cell infusion;
- (3) Subjects should not receive glucocorticoids at a therapeutic dose (defined as prednisone or equivalent > 20 mg/day) and other immunosuppressants within 72 hours prior to CT103A infusion;
- (4) Oxygen saturation $> 91\%$;
- (5) There are no other conditions which, at the discretion of investigators, make the subjects unsuitable for apheresis.

3.3 Study Stopping Criteria and withdrawal from the study

3.3.1 Study Stopping Criteria

The study can be terminated/suspended in the following ways:

- (1) The sponsor has the right to terminate/suspend the trial. Before terminating/suspending a clinical trial, the sponsor must notify the investigator, the ethics

committee, the institution, and the regulatory authority(ies) concerned, and state the reasons. After early termination/suspension of the study, restarting the study must be approved by the ethics committee.

- (2) Termination/suspension required by the ethics committee.
- (3) Termination/suspension required by the data monitoring committee (DMC).

Reasons for termination/suspension may include, but are not limited to, the following:

- (1) The number and severity of adverse events occurring in this study indicate that continuation of the study would cause significant harm to the subjects;
- (2) The quality of the clinical data already obtained is poor and not conducive to continuing further research;
- (3) The study is terminated due to changes in regulatory policy and regulations.

3.3.2 Dropout/ End of Study

Dropout refers to the situation where a subject in the study no longer undergoes efficacy evaluation due to disease progression, starting a new anti-myeloma treatment or other reasons. The subject will receive a dropout visit and undergo the follow-up as specified in this protocol.

End of study (EOS) refers to the situation where a subject withdraws from the study due to CT103A cell manufacturing failure, failure to receive CT103A infusion, withdrawal of informed consent, death, loss to follow-up, study termination by the sponsor or other reasons (except for disease progression or starting a new anti-tumor treatment). Except for death and loss to follow-up, an EOS visit should be performed whenever possible. Subjects who have not received the cell infusion are not required to undergo an EOS visit.

All subjects have the right to withdraw informed consent and withdraw from the study at any time without discrimination or retaliation. The investigator should clearly record the reasons and time of ICF withdrawal, observe and assess the subjects accordingly, and complete the dropout/EOS visit (if possible before withdrawal the ICF) as specified in the protocol.

All subjects who withdraw from the study due to TRAE should be followed until the adverse event has returned to baseline or stabilized. Adverse events that, in the judgment of the investigator, cannot be further recovered may not be further followed. In this case, the investigator must record his or her assessment in the subject's source document.

During the study, for all subjects who have received the treatment but failed to complete relevant study procedures specified in the protocol, the investigator should contact the subjects who did not complete the visit as required and record the evidence of contact in corresponding source document (e.g., the time and date of the telephone contact and relevant evidence of communication).

For any reason, the source document and electronic case report form (eCRF) should be retained for subjects who withdraw from the study.

4. Study Treatment

4.1 Treatment drugs

4.1.1 Investigational Product (IP)

- IP name: Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A);
- Dose: 1.0×10^6 CAR-T cells/kg (tolerance of $\pm 30\%$);
- Major component: Fully human BCMA chimeric antigen receptor autologous T cells;
- Name of excipients: Multiple electrolyte injection, human albumin, glucose injection, vitamin C injection, compound amino acid injection (18AA-II), dimethyl sulfoxide;
- Pack size: 1.0×10^6 CAR-T cells/kg, 20 mL; determined according to the subject's body weight and the effective content of the cell product;
- Appearance: White or slightly yellow frozen solid, slightly yellow suspension after thawing;
- Storage and transport conditions: Store in a gas-phase liquid nitrogen tank ($< -130^\circ\text{C}$); transport in a gas-phase liquid nitrogen tank ($< -130^\circ\text{C}$);
- Manufacturer: Nanjing IASO Medical Technology Co., Ltd.; Nanjing IASO Biotechnology Co., Ltd.;

4.1.2 Lymphodepletion regimen

Cyclophosphamide 500 mg/m^2 administered by intravenous infusion over 30 minutes daily for three consecutive days, followed by fludarabine 30 mg/m^2 administered by intravenous infusion over 30 minutes daily for three consecutive days.

If the subject has renal impairment or other conditions that require adjustment of the dose of the lymphodepleting medication, the investigator may adjust the dose of lymphodepletion drugs after comprehensive assessment and confirmation with the sponsor.

4.1.3 Bridging therapy

After apheresis and before lymphodepletion, bridging therapy may be used to maintain disease stability at the discretion of the investigator, and the decision to use bridging therapy will be made with the approval of the sponsor. Bridging therapy must be a short-term treatment previously received by the subject and should not be an anti-CD38 monoclonal antibody. Pre-lymphodepletion assessments will be performed at least 7 days after bridging therapy. Lymphodepleting chemotherapy is not allowed in subjects who have achieved CR or better according to IMWG (2016) criteria after bridging therapy.

4.2 Method and Precautions for Administration

4.2.1 Administration Method

After the lymphodepleting chemotherapy, through the pre-infusion assessment, subjects who, in the investigator's judgment, are suitable to be treated will receive CT103A cell infusion.

1. Prophylactic medication: Promethazine 25 mg or diphenhydramine 20 mg is allowed to be intramuscularly injected 15 to 30 minutes before CT103A infusion. Acetaminophen or other non-steroidal anti-inflammatory drugs are administered if fever (not due to infection) occurs. As glucocorticoids may affect T cell persistence, systemic glucocorticoids such as hydrocortisone, prednisone, methylprednisolone, or dexamethasone should be avoided except in life-threatening emergencies.
2. Transportation of IP: CT103A cells are stored and transported in gas-phase liquid nitrogen, and delivered to clinical sites in gas-phase liquid nitrogen below -130°C.
3. IP thawing: Thawing is performed according to the Standard Operating Procedure (SOP) or the pharmacy manual. If the package is damaged, leaking or shows signs of damage, the infusion is prohibited, and it will be handled according to the SOP;
4. Infusion of IP: The infusion is performed according to the IP infusion SOP;
5. During the infusion period, emergency facilities should be available so that any severe allergic reaction, severe hypotension, or other reactions can be treated in a timely manner. Vital signs (temperature, respiratory rate, heart rate, blood pressure) should be measured at 15 ± 3 min pre-infusion, at the start of the infusion, and within one hour after infusion (every 15 ± 3 minute). Abnormal vital signs should be monitored until the measurements are stable and in a safe state.

4.2.2 Dose Adjustment and Drug Discontinuation as Indicated

4.2.2.1 Dose Delay and Dose Adjustment

1. Subjects should be assessed for lymphodepletion criteria prior to lymphodepleting chemotherapy. If the subject does not meet the criteria for lymphodepletion, lymphodepletion may be delayed up to 8 weeks until the subject meets the criteria for lymphodepletion.
2. Subjects must be assessed prior to infusion. If the subject does not meet the criteria for cell infusion, the infusion may be delayed for up to 2 weeks. If the delay exceeds 2 weeks, the investigator will assess whether the subject should undergo a repeat pre-lymphodepletion assessment and/or lymphodepletion procedure.
3. Adjustment of CT103A dose is not permitted, but a tolerance of $\pm 30\%$ is acceptable.
4. The safety and preliminary efficacy of CT103A at a dose of 0.5×10^6 CAR-T cells/kg in the treatment of RRMM has been demonstrated in previous clinical studies. Therefore, in order to maximize the benefit to the subjects, if the number of CAR-T cells produced is inadequate for the CT103A dose (at least $\geq 0.5 \times 10^6$ CAR-T cells/kg), the infusion may be conditionally administrated provided that the

criteria for infusion are met after a discussion between the investigator and the sponsor and a full evaluation of the safety of the IP and the condition of the subject.

4.2.2.2 Criteria for Discontinuation of Administration

If a grade 4 infusion-related or allergic reaction occurs, the subject should immediately stop the infusion and receive symptomatic treatment. The investigator will decide whether to withdraw the subject from the study treatment.

4.2.3 Precautions

1. The IP is an autologous cell therapy product. Before the infusion, two investigators are needed to check the identification information with the subject separately and individually to verify the subject's identity.
2. The IP should be administered in a hospital setting.
3. Clean tap water or autoclaved sterile water should be used for the water bath to revive of the IP.
4. Prior to the IP infusion, the following aspects should be confirmed first: correct name and identification, within the expiry date, complete without cracks and under sealed status.
5. The appearance of the IP is white or slightly yellow frozen solid, slightly yellow suspension after thawing. Before intravenous use, the IP should be observed for precipitation, flocculation, and crystallization. If any of the above phenomena are observed, administration to subjects should be suspended. At the same time, the sponsor should be informed of the abnormality in a timely manner and the condition will be managed according to the sponsor's feedback and suggestions.
6. The IP is stored in liquid nitrogen, and delivered and transported to each site in gas-phase liquid nitrogen below -130°C. If there is an abnormal temperature during the storage or transportation, the IP should be transferred to the specified temperature as soon as possible, and the administration to subjects should be suspended; at the same time, the sponsor should be informed of the abnormal temperature range and duration of the abnormality in a timely manner, and the condition will be handled according to the sponsor's feedback and suggestions.
7. The IP is infused using a disposable blood transfusion set.
8. After thawing in a water bath, the IP should be infused immediately. If the intravenous infusion cannot be immediately performed due to reason related to the subject or any other reasons and the delay in infusion exceeds 2 hours, the IP should be returned to the sponsor for destruction.
9. As the IP are genetically modified autologous T cells, on the surface of which the anti- BCMA CAR structure is expressed, allergic reactions may be induced during the administration. Antiallergic agents should be readily available (systemic use of glucocorticoids is not recommended except in life-threatening emergencies).
10. Hypotension may occur during the infusion; therefore, it is recommended to

discontinue antihypertensives within 12 hours before the treatment and throughout the infusion.

11. The IP may induce arrhythmia, thus subjects with a history of heart disease should be closely monitored when receiving the treatment.
12. Blood counts and platelet counts should be monitored on a regular basis during the study, and subjects with symptoms of hypocytosis should be closely monitored.
13. The use of the IP should not be continued if it is beyond the expiry date on the drug label.

4.3 Concomitant Treatments

Concomitant medications and concomitant treatments refer to the concurrent use of two or more medications/treatments. Concomitant medications and treatments are defined as drugs (including chemical drugs, biological products, and patent medicines) or treatments other than the IP in the study.

The collection of concomitant treatments starts from the ICF signing until 2 years after CT103A cell infusion (if PFS $\geq$ 24 months) or until the dropout visit (24 months $>$ PFS $\geq$ 6 months), whichever occurs first. If the disease progression occurs within 6 months after CT103A cell infusion, efforts should be made for the collection until 6 months after the cell infusion. Subjects who have entered the long-term follow-up period are required to be followed for subsequent concomitant treatments for CT103A-related AEs/SAEs.

All concomitant medications (including permitted and prohibited concomitant medications) and treatments should be recorded in the source document and in the eCRF, and the following information should be recorded in detail in the source document and in the eCRF: drug/non-drug name, reason for medication, dose, unit, dosing frequency, route of administration, start date and end date; for concomitant non-drug treatments, the information should include: name of non-drug treatment, treatment description, reason for treatment, treatment start date and end date. If the reason for concomitant medication and treatment meets the definition of an AE, relevant information should also be recorded in the subject's source document and in the eCRF.

4.3.1 Prohibited Concomitant Treatments

1. Other anti-myeloma therapies: During the enrollment of this study and during the study, in addition to the study treatment specified in this clinical study, the subjects should not receive any anti-myeloma treatments (except for bridging therapy and lymphodepleting chemotherapy), including cytotoxic drugs, biologic therapies, immunosuppressants, preventive immunostimulants or any other investigational products.
2. Immunization by vaccination with a live virus.
3. Other treatments that the investigator believes may have an influence on the study assessments.

4.3.2 Permitted Concomitant Treatments

1. The investigator is allowed to administer bridging therapy after apheresis for subjects with high tumor burden or rapid progression during the screening period, but the pre-lymphodepletion assessment should be performed at least 7 days after the bridging therapy.
2. Standard therapy and palliative treatment for pre-existing conditions, medical and/or surgical complications, and all medications should be documented.
3. Relevant medications for the prevention of infusion reactions, the investigator is allowed to administer concomitant treatments for adverse events.
4. If significant neutropenia or febrile neutropenia/infection is observed, the investigator may refer to American Society of Clinical Oncology (ASCO) guidelines to administer corresponding growth factors (e.g., granulocyte colony-stimulating factor [G-CSF]) for prophylactic use.
5. Others: Prophylactic antiemetics, gastric mucosal protection agents, and baseline hypertension medications that, at the discretion of the investigator, can be used concomitantly.

4.4 Receipt and Return of Investigational Products

CT103A cells are stored in liquid nitrogen and are delivered and transported to each site in gas-phase liquid nitrogen below -130°C to avoid shaking. Upon receipt of the IPs by the site, the transportation temperature should be checked and documented in the drug accountability log. The IPs should be checked to ensure that they are correct. Relevant records should be kept in the management files of the study site. In addition, the drug storage temperature should be recorded daily, and contents in the inventory sheet should be recorded: the date of receipt of IPs, quantity, batch number, the dispensed quantity, and the inventory quantity.

All the IPs are accessible only to the authorized personnel. After being thawed in a water bath, the IP should be infused immediately. If the intravenous infusion cannot be immediately given for any reason and is subsequently delayed for over two hours, the IP should be returned to the sponsor for destruction.

After completion of the infusion, the bag should be destroyed according to site SOP.

4.5 Subject Allocation

The study design is sequential enrollment and eligible subjects will be enrolled one after another for single-dose administration. For newly initiated sites, there should be at least 14 days between infusions of the first three subjects.

5. Visit Schedule

5.1 Screening Period and Enrollment Period (-8w to -18d)

5.1.1 Screening Period

The following information/assessments will be collected at the time of screening:

- (1) ICF signing
- (2) Review of inclusion/exclusion criteria
- (3) Collection of demographic information: During the screening period, the history of multiple myeloma needs to be collected in detail regarding the history of tumor diagnosis and treatment, including but not limited to:
 - Tumor diagnosis, classification and staging, and grading of degree of risk at initial diagnosis and screening.
 - Prior anti-myeloma therapies (including treatment regimen, drug name, start and end dates of each medication, reason for treatment, reason for discontinuation of each medication, best response achieved with each treatment regimen).
 - Tumor-related radiotherapy (including body site, total dose, unit, start and end times, reason for treatment, best response achieved, and date of progression at the radiation site during or after the treatment).
 - Symptoms and signs pre-dose, including the progression of medical history and disorders.
- (4) Height and weight
- (5) Physical examination
- (6) Vital signs
- (7) Echocardiography
- (8) 12-lead ECG (all subjects should be measured after at least 5 minutes of rest, and HR, PR interval, RR interval, QRS duration, heart rate-corrected QT interval [QTcF] using the Fridericia formula should be recorded)
- (9) Oxygen saturation test
- (10) Blood pregnancy test in women of childbearing potential
- (11) Virology/syphilis testing
- (12) Hematology
- (13) Blood biochemistry
- (14) Urinalysis
- (15) Coagulation

- (16) Peripheral blood smear
- (17) Serum calcium and corrected calcium
- (18) β 2-microglobulin
- (19) Serum immunoglobulin quantification
- (20) Serum free light chain assay
- (21) Serum protein electrophoresis (SPEP)
- (22) Serum immunofixation electrophoresis (SIFE)
- (23) 24-hour urine M protein quantification
- (24) 24-hour urine light chain quantification
- (25) Urine protein electrophoresis (UPEP)
- (26) Urine immunofixation electrophoresis (UIFE)
- (27) Imaging-based assessment: Low-dose whole-body CT or PET-CT can be performed for skeletal survey during the screening period, if low-dose whole-body CT or PET-CT is not available, local CT/MRI can be performed instead. In addition to the examination during the screening period, the imaging-based assessments at other visits should be done if extramedullary disease (EMD) is present prior to cell infusion or as determined by the investigator based on the clinical indications of the subjects (e.g., suspected achievement of CR or disease progression). The examination method for each part of the same subject during the follow-up period should be consistent. For subjects who have a mass as detected by CT or MRI that is inconsistent with the investigator's assessment, PET-CT may be added to assess the tumor activity. Imaging examination results within 4 weeks prior to ICF signing are acceptable;
- (28) Bone marrow aspiration includes: bone marrow smear, bone marrow biopsy pathology + immunohistochemistry, cytogenetics (FISH), and bone marrow flow immunophenotyping assay (including MRD testing). Recommendations for bone marrow immunohistochemistry include but are not limited to BCMA (initial), CD19, CD20, CD38, CD56, CD138, κ light chain, and λ light chain. Bone marrow flow cytology with more than 8 colors of antibody markers is recommended, including but not limited to BCMA, CD19, CD38, CD45, CD56, CD20, CD138, cytoplasmic κ light chain, cytoplasmic λ light chain. Bone marrow immunohistochemistry or bone marrow flow cytology may be performed during the screening phase. Cytogenetic testing is performed by FISH (CD138+ magnetic bead sorting of myeloma cells or concurrent cytoplasmic immunoglobulin staining is recommended to differentiate plasma cells). Suggested loci for detection include but are not limited to IgH translocation, 17p- (p53 deletion), 13q14 deletion, 1q21 amplification, and if FISH is positive for IgH translocation, further testing is recommended for t(4;14), t(11;14), t(14;16), t(14;20), cytogenetic testing is only required in the screening period; If the screening test fails or is not detected, it can be repeated at the initial

visit; bone marrow examination results within 2 weeks before ICF signing are acceptable in the screening period (but the examination items must meet the requirements of this study, and new samples must be obtained in case of missing items);

(29) Peripheral blood-free BCMA;

(30) Recording of adverse events (AEs) and serious adverse events (SAEs):

(31) Documentation of concomitant treatments

Note:

- If a subject has confirmed non-secretory multiple myeloma at screening and baseline, tests (19) through (26) may not be performed at subsequent follow-up visits.
- This study allows for a repeat test during the screening period, including but not limited to a repeat test due to laboratory test abnormality or an error in a test value, and the last test result obtained after supportive treatment and a repeat test will be used to determine whether the subject is eligible for enrollment in this study.
- Screening failures are allowed to be re-screened. At the re-screening, the ICF should be re-signed, and a new subject number will be assigned.
- The same subject can only have one repeat test or be re-screened once.

5.1.2 Enrollment

During the screening period, the subjects will complete corresponding contents of examination according to the visit schedule and will be assigned an enrollment number after meeting the eligibility criteria as assessed by the investigator.

5.2 Apheresis (-8w to -18d)

Apheresis will be performed for the preparation of cells. Within 1 day before apheresis, all test results at the apheresis visit should be assessed. If blood biochemistry, coagulation function and urinalysis have been performed within 7 days, corresponding tests are not required at the visit.

Apheresis is performed according to institutional practice standard, and the target is that the apheresis sample transported to the manufacturing site contains $> 1 \times 10^9$ ($> 2 \times 10^9$ peripheral blood mononuclear cells [PBMCs] are recommended to ensure successful cell product manufacturing) PBMCs. In order to achieve this target, a second run of apheresis collection may be performed.

If the subject has a high tumor burden or rapidly progressing disease, the investigator may decide to use bridging therapy after apheresis.

The following information/assessments will be collected at the time of apheresis:

- (1) Body weight
- (2) Vital signs
- (3) Hematology
- (4) Safety laboratory tests for blood biochemistry (fasting), coagulation, and urinalysis

- (5) Review the criteria for apheresis
- (6) Apheresis samples (additional 3 ml) for exploratory studies
- (7) Recording of adverse events (AEs) and serious adverse events (SAEs)
- (8) Recording of combination treatments.

Second run of apheresis:

Second apheresis is allowed before the baseline assessment in order to ensure at least 1×10^9 PBMCs in the apheresis sample. Before the second run of apheresis collection, it is necessary to review the criteria for apheresis to evaluate whether the subject is suitable for the second apheresis. The second apheresis collection cannot be performed in the following cases:

- The unsuccessful preparation of CAR-T cells is due to the quality issue of the subject's own mononuclear cells.
- The unsuccessful preparation of CAR-T cells is due to the failure in meeting the criteria for apheresis.
- Conditions which, in the investigator's comprehensive assessment, rendered the subject unsuitable for the second apheresis collection.

5.3 Baseline Assessment Visit (Within 7 Days prior to lymphodepletion)

Baseline assessment (pre-lymphodepletion assessment) should be performed within 7 days prior to the lymphodepletion, except that the vital signs and physical examination should be performed within 1 day prior to the lymphodepletion. Pre-lymphodepletion assessment requires that the subject has not achieved a complete response (CR), this assessment may be confirmed by local laboratory results, but central laboratory results which are considered as baselines should be completed at the same time.

Baseline tumor burden assessment within 14 days prior to the start of lymphodepletion are acceptable, except for the bone marrow aspiration/biopsy-related assessments within 4 weeks are acceptable. Prior to lymphodepletion, the appropriate tests should be repeated to confirm that subjects meet the criteria for lymphodepletion.

The baseline assessment visit includes the following:

- (1) Physical examination
- (2) Vital signs
- (3) 12-lead electrocardiogram
- (4) Echocardiography
- (5) Oxygen saturation
- (6) Safety laboratory tests of blood (collected at the same time as PK blood, with a maximum time difference of 24 hours), blood biochemistry (fasting), coagulation, and urinalysis
- (7) Inflammatory factors

- (8) Peripheral blood smear
- (9) Serum calcium and albumin-corrected calcium
- (10) β 2-microglobulin
- (11) Serum immunoglobulin quantification
- (12) Serum free light chain assay
- (13) Serum protein electrophoresis (SPEP)
- (14) Serum immunofixation electrophoresis (SIFE)
- (15) 24-hour urine M protein quantification
- (16) 24-hour urine light chain quantification
- (17) Urine protein electrophoresis (UPEP)
- (18) Urine immunofixation electrophoresis (UIFE)
- (19) Bone marrow aspiration
- (20) Pregnancy Test (women of childbearing age only)
- (21) Peripheral blood free BCMA
- (22) Immunogenicity testing
- (23) RCL
- (24) PK Blood Collection (an additional 3 ml should be collected for exploratory studies)
- (25) VCN
- (26) Peripheral blood BCMA CAR T-cell assay
- (27) Lentiviral genomic insertion site assay
- (28) Concomitant treatment/adverse event/serious adverse event recording

5.4 Lymphodepleting chemotherapy (-7d~-2d)

The lymphodepleting chemotherapy will be performed within 1 week before the cell infusion. Height/weight/body surface area measurements are performed before the lymphodepletion. The visit included the following:

- (1) Review the criteria for lymphodepletion
- (2) Height/weight/body surface area
- (3) Pretreatment dosing
- (4) Record concomitant treatment/ AE/ SAE

5.5 Pre-infusion Assessment (-1D)

If the subject does not meet the criteria for cell infusion, the investigator may provide symptomatic treatment until the subject's status is recovered so that cell infusion can be

performed. Delayed cell infusion should not exceed 2 weeks. The pre-infusion assessment visit will include the following:

- (1) Body weight
- (2) Physical examination
- (3) Vital signs and ECOG score
- (4) 12-lead electrocardiogram
- (5) Echocardiography: depending on clinical indications, echocardiography may be added at the discretion of the investigator if the subject develops signs or symptoms such as heart failure
- (6) Oxygen saturation testing
- (7) Blood pregnancy test (women of childbearing age only)
- (8) Safety laboratory tests for hematology, blood biochemistry (fasting), coagulation, and urinalysis
- (9) Inflammatory Factors: should include at least IL-6, CRP, and ferritin
- (10) Record concomitant treatment/ AE/ SAE

5.6 CT103A Infusion (D0)

The cell infusion visit should be performed while the subject is hospitalized.

- (1) Review criteria for cell infusion
- (2) Vital signs

On the day of CT103A cell infusion, vital signs (temperature, respiratory rate, heart rate, blood pressure) should be measured at 15 ± 3 minutes before the start of cell infusion, at the start of cell infusion and within 1 hour (every 15 ± 3 minutes) after cell infusion ([Table 2](#)).

Table 2 Requirements for monitoring vital signs

Time	Before the Start of Cell Infusion	At the Start of Cell Infusion	After the Start of Cell Infusion			
	-15 $\pm$ 3 min	0 min	15 $\pm$ 3 min	30 $\pm$ 3 min	45 $\pm$ 3 min	60 $\pm$ 3 min
Temperature	√	√	√	√	√	√
Blood pressure	√	√	√	√	√	√
Respiration	√	√	√	√	√	√
Heart rate	√	√	√	√	√	√

Note:

First aid facilities should be available during cell infusion for timely treatment of severe allergic reactions, severe hypotension, or other reactions. Body temperature should be measured twice daily (at least 6 hours between measurements) until D28 and, if the temperature is abnormal, closely monitored until it is normal. If the subject is discharged during this period, a thermometer should be issued to record the temperature daily and recorded on the patient record card.

- (1) Hematology
- (2) 12-lead ECG
- (3) Echocardiography
- (4) Blood pregnancy test (women of childbearing age only)
- (5) Medications to prevent infusion-related reactions
- (6) CT103A cell infusion
- (7) Record concomitant treatment/adverse event/serious adverse event.

5.7 Primary follow-up period (1d~ 2 years post-infusion)

5.7.1 Hospitalization period and visits within D28 (1d~28d)

The hospitalization period should be at least 14 days, and the hospitalization from 15d to 28d should be performed per local site regulations. The window period for 7d, 10d and 14d visits is ± 12 h, and is ± 2 d for 21d and 28d visits. The visits include the following:

- (1) Physical examination/ vital signs/ECOG score: 1d, 4d, 7d, 10d, 14d, 21d, 28d;
- (2) 12-lead electrocardiogram: 1d, 7d, 14d, 28d;
- (3) Echocardiography: depending on clinical indications, echocardiography may be added at the discretion of the investigator if the subject develops signs or symptoms such as heart failure;
- (4) Oxygen saturation test: 1d, 4d, 7d, 10d, 14d, 21d, 28d; oxygen saturation is measured at least twice daily during CRS (2 measurements must be separated by at least 6 hours).
- (5) Blood pregnancy test (women of childbearing potential only): According to clinical indications, women of childbearing potential should be retested promptly if they have suspected pregnancy, such as menopause, vomiting, abdominal pain, and vaginal bleeding;
- (6) Hematological test: 1d, 4d, 7d, 10d, 14d, 21d, 28d. Samples should be collected at the same time as PK blood, and the maximum difference in collection time should not exceed 24 hours.
- (7) Blood biochemistry (fasting): 7d, 14d, 21d, 28d;
- (8) Urinalysis: 7d, 14d, 21d, 28d;
- (9) Coagulation function: 7d, 14d, 21d, 28d;
- (10) Serum calcium and albumin-corrected calcium: 14d, 28d;

- (11) Inflammatory factors: 1d, 4d, 7d, 10d, 14d, 21d, 28d
- (12) Peripheral blood smear: 14d, 28d
- (13) β 2-microglobulin test: 14d, 28d
- (14) Serum immunoglobulin quantitation: 14d, 28d
- (15) Serum Free Light Chain Quantification: 14d, 28d
- (16) Serum protein electrophoresis: 14D, 28D
- (17) Serum immunofixation electrophoresis: 14d, 28d
- (18) 24h urine M-protein quantification: 14d, 28d
- (19) 24-hour urine light chain quantification: 14d, 28d
- (20) Urine protein electrophoresis: 14d, 28d
- (21) Urine protein immunofixation electrophoresis: 14d, 28d;
- (22) Bone marrow aspiration/biopsy: 14d, 28d (including smear, bone marrow biopsy pathology + immunohistochemistry, and bone marrow flow immunophenotyping [including MRD testing]);
- (23) Peripheral blood BCMA CAR-T cell assays: 1d, 4d, 7d, 10d, 14d, 21d, 28d;
- (24) Peripheral blood free BCMA assays: 1d, 4d, 7d, 10d, 14d, 21d, 28d;
- (25) Immunogenicity assay: 28d;
- (26) PK blood sampling (additional 3 ml for exploratory studies): 1d ($\pm$ 1 h), 4d ($\pm$ 3 h), 7d ($\pm$ 12 h), 10d ($\pm$ 12 h), 14d ($\pm$ 12 h), 21d ($\pm$ 2 d), 28d ($\pm$ 2 d).
- (27) VCN assay: 1d, 4d, 7d, 10d, 14d, 21d, 28d. Using ddPCR assay.
- (28) Lentiviral genomic insertion site assay: 14d, 28d;
- (29) IMWG efficacy assessment: 14d, 28d.
- (30) Record concomitant treatment/adverse event/serious adverse event.

5.7.2 Post-treatment follow-up period

Subjects will be assessed and continue to have follow up visits at 2m (D60), 3m (D90) after cell infusion, and every 3 months thereafter until disease progression, initiation of subsequent anti-myeloma therapy, withdrawal of ICF, withdrawal from the study, death, loss to follow-up, 2 years after cell infusion, or study termination, whichever occurs first.

The visits include the following contents:

- (1) Physical examination/vital signs/ECOG score: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (2) Echocardiography: Depending on clinical indications, echocardiography may be added at the discretion of the investigator if the subject develops signs or symptoms such as heart failure;

- (3) 12-lead ECG: 2m (60d), 3m (90d), and then every 3 months (90 days) until 2 years after the exit visit or cell return, whichever comes first;
- (4) Blood Pregnancy Test (women of childbearing potential only): Based on clinical indications, women of childbearing potential should be retested promptly if they experience suspected pregnancy, such as menopause, vomiting, abdominal pain, or vaginal bleeding;
- (5) Hematological tests: 2m (60d), 3m (90d), and then every 3 months (90)
- (6) Fasting blood biochemistry: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (7) Urinalysis: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (8) Coagulation: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (9) Serum calcium and albumin-corrected calcium: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (10) Inflammatory factors: 2m (60d), 3m (90d);
- (11) Peripheral blood smear: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (12) β 2-microglobulin test: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (13) Serum immunoglobulin quantification: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (14) Serum free light chain quantification: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (15) Serum protein electrophoresis: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (16) Serum immunofixation electrophoresis: 2m (60d), 3m (90d), and then every 3 months;
- (17) 24-hour urine M-protein quantification: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (18) 24-hour urine light chain quantification: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (19) Urine protein electrophoresis: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (20) Urine protein immunofixation electrophoresis: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (21) Bone marrow aspiration: 2m (60d), 3m (90d), and then every 3 months (90 days);
- (22) Peripheral blood free BCMA assay: 2m (60d), 3m (90d) and then every 3 months (90 days).
- (23) Immunogenicity testing: 3m (90d), 6m (180d), 12m (360d), 24m (720d);
- (24) RCL test: 3m (90d), 6m (180d), 12m (360d), 24m (720d);

- (25) Lentiviral genomic insertion site assays: 3m (90d), 6m (180d), 12m (360d), 24m (720d); no testing is required if VCN test values are below the lower limit of detection. The product will be monitored for tumorigenic risk over time in this protocol to assess the risk of clonal dominant hyperplasia and long-term safety. If subjects develop clonal growth of vector-positive cells, or if the test reveals gene integration sites near oncogenes or cancer-associated genes, the testing interval should be shortened to no more than 3 months and subjects should be closely monitored for signs of malignancy until the lentiviral vector is no longer detectable or there are good reasons to exclude the risk of malignancy;
- (26) PK blood collection (an additional 3 ml should be collected for exploratory studies): 60 d ($\pm$ 14 days), 90 d ($\pm$ 14 days), and every 3 months thereafter (every 90 days, $\pm$ 14 days);
- (27) IMWG efficacy assessment: 2m (60d), 3m (90d), and every 3 months (90 days) thereafter;
- (28) Record concomitant treatment/adverse event/serious adverse event.

5.8 Long-term follow-up period

5.8.1 Long-term follow-up

Subjects who complete the primary follow-up period of 2 years after cell infusion without disease progression will be followed for long-term follow-up every 6 months (180 days $\pm$ 28 days) until disease progression, withdrawal of consent, loss to follow-up, death, or 15 years after cell infusion, whichever occurs first. Follow-up visits will include:

- (1) Peripheral blood smear;
- (2) Serum calcium and albumin corrected calcium;
- (3) β 2-microglobulin;
- (4) Serum immunoglobulin quantification;
- (5) Serum free light chain quantification;
- (6) Serum protein electrophoresis;
- (7) Serum immunofixation electrophoresis;
- (8) 24-hour urine M-protein quantification;
- (9) 24-hour urine light chain quantification;
- (10) Urine protein electrophoresis;
- (11) Urine protein immunofixation electrophoresis;
- (12) Bone marrow aspiration: Including bone marrow smear, bone marrow biopsy pathology + immunohistochemistry, bone marrow flow immunophenotyping (including MRD testing);
- (13) IMWG efficacy assessment;

- (14) PK blood collection;
- (15) VCN: Every 6 months for 5 years after cell infusion, regardless of whether the VCN is below the lower limit of detection; every 12 months for 5 to 15 years after cell infusion until the end of the study or 2 consecutive VCN tests below the lower limit of detection, whichever occurs first; if the last two VCN tests within 4-5 years after cell infusion are below the lower limit of detection, then VCN testing is not required at the 5-15 year follow-up visits;
- (16) Peripheral blood free BCMA assay: until the dropout visit or the end of the study, whichever comes first;
- (17) Lentiviral genomic insertion site assay;
- (18) RCL test;
- (19) AEs/SAEs: Collect adverse events, serious adverse events (e.g., secondary tumors, etc.) related to the IP, and SAEs for malignancies, neurological, immunogenic or autoimmune diseases, and infections occurring within 5 years, regardless of whether they are related to the IP;
- (20) Concomitant treatment: In addition to the information on combination therapy for CT103A-associated AEs, information on treatment with carcinogenic or mutagenic drugs is also required. Carcinogenic or mutagenic drugs are defined as drugs for which the package insert suggests carcinogenic or mutagenic effects, excluding drugs used for short-term or infrequent use such as narcotics, radioisotope labeled contrast agents and corticosteroids (unless the investigator believes there is a potential carcinogenic or mutagenic risk);
- (21) Subsequent anti-myeloma treatment: including drug/non-drug treatments related to the study disease, such as radiotherapy, chemotherapy, hematopoietic stem cell transplantation (HSCT) therapy, gene therapy, surgery, and any other anti-tumor treatment, with gene therapy to be clarified if viral vectors are used.

5.8.2 Post-dropout follow-up

Subjects who withdraw from the study during the primary follow-up period should be followed until withdrawal of consent, loss to follow-up, death, or 15 years after cell infusion, whichever occurs first.

Follow-up within 5 years after cell infusion

Subjects who have completed a dropout visit will be followed up every 6 months from the date of the dropout visit until 5 years after the cell infusion. If the dropout visit is later than 5 years after the cell infusion, the follow-up will not occur at this stage and will proceed directly to the 5-15 year follow-up after the cell infusion. The following information/assessments will be collected at the visits between the dropout visit and 5 years after the cell infusion:

- (1) VCN testing: Every 6 months regardless of whether the VCN test is below the lower limit of detection;

- (2) Lentiviral genomic insertion site assay;
- (3) RCL test;
- (4) AEs/SAEs: Collect adverse events, serious adverse events (e.g., secondary tumors, etc.) related to the IP, and SAEs for malignancies, neurological, immunogenic or autoimmune diseases, and infections occurring within 5 years, regardless of whether they are related to the IP;
- (5) Concomitant treatment: In addition to the information on combination therapy for CT103A-associated AEs, information on treatment with carcinogenic or mutagenic drugs is also required. Carcinogenic or mutagenic drugs are defined as drugs for which the package insert suggests carcinogenic or mutagenic effects, excluding drugs used for short-term or infrequent use such as narcotics, radioisotope labeled contrast agents and corticosteroids (unless the investigator believes there is a potential carcinogenic or mutagenic risk);
- (6) Pregnancy information: Pregnancies and births of subjects and their spouses must be recorded. If a pregnancy occurs, it must be reported to the sponsor or its designated representative within 24 hours of awareness, and the outcome of the pregnancy must be followed up (at least one month after the fetus is born);
- (7) Survival information: information on the subject's survival should be updated every six months or collected by telephone, questionnaire, or other lawful methods if the subject does not come back to the sites for follow-up; if the subject dies, the time and cause of death should be recorded if possible;
- (8) Subsequent anti-myeloma treatment: includes drug/non-drug treatments related to the study disease, such as radiotherapy, chemotherapy, hematopoietic stem cell transplantation (HSCT) therapy, gene therapy, surgery, and any other anti-tumor treatment, with gene therapy to be clarified if viral vectors are used.

Follow-up 5 to 15 years after cell infusion

Subjects who have completed a dropout visit will be followed up by telephone or questionnaire every 6 months from 5 to 15 years after cell infusion and at the study site every 12 months. The following information/assessments will be collected at the 5-15 year visits:

- (1) VCN testing: Every 12 months until 15 years after cell infusion, two consecutive test results are below the lower limit of detection, whichever comes first. If the last two VCN tests are below the lower limit of detection within 4-5 years after cell infusion, VCN testing is not required at the 5-15 year follow-up visits;
- (2) Lentiviral genomic insertion site assay;
- (3) RCL test;
- (4) AEs/SAEs: Collect adverse events, serious adverse events (e.g., secondary tumors, etc.) related to the IP, and SAEs for malignancies, neurological, immunogenic or autoimmune diseases, and infections occurring within 5 years, regardless of whether

they are related to the IP;

- (5) Concomitant treatment: In addition to the information on combination therapy for CT103A-associated AEs, information on treatment with carcinogenic or mutagenic drugs is also required. Carcinogenic or mutagenic drugs are defined as drugs for which the package insert suggests carcinogenic or mutagenic effects, excluding drugs used for short term or infrequent use such as narcotics, radioisotope labeled contrast agents and corticosteroids (unless the investigator believes there is a potential carcinogenic or mutagenic risk);
- (6) Pregnancy information: Pregnancies and births of subjects and their spouses must be recorded. If a pregnancy occurs, it must be reported to the sponsor or its designated representative within 24 hours of awareness, and the outcome of the pregnancy must be followed up (at least one month after the fetus is born);
- (7) Survival information: Information on the subject's survival should be updated every six months or collected by telephone, questionnaire, or other lawful methods if the subject does not come back to the sites for follow-up; if the subject dies, the time and cause of death should be recorded if possible;
- (8) Subsequent anti-myeloma treatment: Including drug/non-drug treatments related to the study disease, such as radiotherapy, chemotherapy, hematopoietic stem cell transplantation (HSCT) therapy, gene therapy, surgery, and any other anti-tumor treatment, with gene therapy to be clarified if viral vectors are used.

5.9 Dropout/End of study

5.9.1 Dropout

Dropout refers to the situation where a subject in the study no longer undergoes efficacy evaluation due to disease progression, starting a new anti-myeloma treatment or other reasons. The subject will receive a dropout visit and undergo the follow-up as specified in this protocol.

If a new anti-myeloma therapy has been started prior to the dropout visit, unless the subject withdraws the ICF, all items of the dropout visit should be completed within the time window as far as possible, with detailed chronological documentation of the external diagnostic basis for disease progression and the course of anti-myeloma therapy. The efficacy assessment should not be repeated within 4 weeks of the last confirmed efficacy assessment at two consecutive visits; other tests should not be repeated within 1 week of the last test; and the RCL test at the dropout visit should not be repeated within 1 year of the last test after infusion.

If a subject does not have a dropout visit at the required time, it is considered an unscheduled visit. The dropout visit includes the following contents:

- (1) Physical examination/ vital signs/ECOG score (if visit is within 2 years of CT103A cell infusion);
- (2) Hematology (if visit is within 2 years of CT103A cell infusion)

- (3) Blood biochemistry (if visit is within 2 years of CT103A cell infusion)
- (4) Urinalysis (if visit is within 2 years of CT103A cell infusion)
- (5) Coagulation (if visit is within 2 years of CT103A cell infusion)
- (6) Virology/syphilis testing
- (7) Echocardiography (if visit is within 2 years of CT103A cell infusion)
- (8) 12-lead electrocardiogram (if visit is within 2 years of CT103A cell collection)
- (9) Peripheral blood smear
- (10) Serum calcium and albumin corrected calcium;
- (11) β 2-microglobulin;
- (12) Inflammatory factors (if visit is within 2 years of CT103A cell infusion)
- (13) Serum immunoglobulin quantification
- (14) Serum free light chain quantification;
- (15) Serum protein electrophoresis;
- (16) Serum immunofixation electrophoresis;
- (17) 24-hour urine M protein quantification;
- (18) 24-hour urine light chain quantification
- (19) Urine protein electrophoresis;
- (20) Urine protein immunofixation electrophoresis;
- (21) Bone marrow aspiration: including bone marrow smear, bone marrow biopsy pathology + immunohistochemistry, bone marrow flow immunophenotyping (including MRD testing); Bone marrow aspiration may not be needed if blood and urine tests are clear of disease progression).
- (22) Peripheral blood free BCMA assay
- (23) Peripheral blood BCMA CAR T-cell assay
- (24) Immunogenicity assay (if visit is within 2 years of CT103A cell infusion)
- (25) RCL assay
- (26) PK blood collection (an additional 3 ml to be collected for exploratory studies)
- (27) VCN assay;
- (28) Lentiviral genomic insertion site assay;
- (29) IMWG efficacy assessment;
- (30) Blood pregnancy test (if visit is within 2 years of CT103A cell infusion);
- (31) Concomitant treatment;
- (32) Adverse events;

- (33) Serious adverse events;
- (34) Subsequent anti-myeloma treatment.

5.9.2 End of study

End of study (EOS) refers to the situation where a subject withdraws from the study due to CT103A cell manufacturing failure, failure to receive CT103A infusion, withdrawal of informed consent, death, loss to follow-up, study termination by the sponsor or other reasons (except for disease progression or starting a new anti-tumor treatment). Except for death and loss to follow-up, an EOS visit should be performed whenever possible. Subjects who have not received the cell infusion are not required to undergo an EOS visit.

The tests at the EOS visit does not need to be repeated within 1 week of the last test; the RCL test at the EOS visit does not need to be repeated within 1 year of the last test after the cell infusion.

Please refer to the dropout visit for the tests to be completed at the EOS visit. Subjects who dropout due to disease progression or starting a new anti-myeloma therapy and have completed the efficacy assessment at the dropout visit do not need to repeat the efficacy assessment at the EOS visit (items 9-21).

5.10 Unscheduled visits

Unscheduled visits that are performed during the study are required to be recorded in the source document and in the eCRF. At the unscheduled visit, depending on the purpose of the visit, the vital signs, physical examination, adverse events, concomitant medications and treatments as well as their changes that are deemed necessary by the investigator should be recorded. If a subject withdraws from the study at an unscheduled visit, the above contents should be recorded in the source document and in the eCRF.

6. Study Assessment and Procedures

6.1 Safety Assessments

Safety assessments include adverse events, ECOG performance score, laboratory tests, vital signs, physical examination, ECG, and echocardiography.

6.1.1 Adverse Events

A description of adverse events is provided in Section 7 of the protocol.

6.1.2 ECOG performance score

The criteria for ECOG performance score are provided in [Appendix 1](#).

The ECOG performance score visit time points are: Screening period, enrollment period (-8w to -18d), pre-lymphodepletion assessment (within 7 days before lymphodepleting treatment), -1D, D1, D4, D7, D10, D14, D21, D28, 2m, 3m, and once every 3 months thereafter until the drop-out/EOS visit or 2 years after cell infusion (whichever occurs first).

6.1.3 Clinical Laboratory Tests (for Safety Assessments)

Clinical laboratory tests will be performed specifically include the following contents:

➤ Hematology

The test includes red blood cell count, hemoglobin level, red blood cell specific volume, white blood cell count, platelet count, white blood cell classification (including the ratio and absolute count of neutrophils/eosinophils/basophils, lymphocytes/monocytes). Hematology will be performed on the day of infusion according to clinical needs.

➤ Blood chemistry

Blood biochemistry should be performed in the fasting state and should include the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ -GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP or ALP), glucose (Glu), total protein (TP), albumin (ALB), globulin (G), albumin/globulin ratio (A/G), lactate dehydrogenase (LDH), urea/urea nitrogen (Urea/BUN), creatinine (CRE), uric acid (URIC), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), troponin, sodium (Na), potassium (K), magnesium (Mg), chloride (Cl), phosphorus (P).

➤ Urinalysis

The test includes: pH, urinary white blood cells, urinary protein, urinary red blood cells, urinary sugar, ketone bodies, bilirubin, urobilinogen, nitrite, leucocyte esterase; If urine protein $\geq +$ and considered unrelated to the study disease, urine sediment microscopy should be performed, including red blood cell count, white blood cell count, epithelial cells, and bacteria.

➤ Coagulation

The parameters of coagulation include prothrombin time (PT), activated partial

thromboplastin time (APTT), prothrombin time (TT), fibrinogen (FIB), D-dimer and international normalized ratio (INR).

6.1.4 Vital Signs

Test items include temperature, heart rate, respiratory rate, systolic and diastolic blood pressure at rest.

6.1.5 Physical Examination

Physical examination should include at least the following: skin, mucous membranes, lymph nodes, head, neck, chest, abdomen, spine/extremities, and nervous system.

6.2 Efficacy Assessment

6.2.1 Efficacy Assessment Measurements

- Overall response rate (ORR) at 3 months as assessed by the investigators: the proportion of subjects who achieved PR or better at 3 months as defined by the IMWG response criteria;
- Best ORR assessed by the IRC and the investigator: the proportion of subjects who achieved PR or better as defined by the IMWG response criteria;
- Progression-free survival (PFS) as assessed by the IRC and the investigator: Duration from the date of CT103A infusion to the date of first documented evidence of progressive disease or death due to any cause;
- Overall survival (OS): Duration from the start of CT103A treatment to the subject's death (due to any cause);
- Duration of response (DOR) assessed by the IRC and the investigator: Duration from the date of the first documented response (PR or better) to the date of first documented evidence of progressive disease, as defined by the IMWG criteria;
- Time to response (TTR) as assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of the first documented response (PR or better);
- Time to complete response (TTCR) assessed by the IRC and the investigator: Time interval from the date of CT103A infusion to the date of first documentation of a complete response (CR) or stringent complete response (sCR);
- MRD response assessment: The proportion of subjects achieving MRD-negativity and the duration of MRD-negativity.

6.2.2 Efficacy Assessment Criteria

Refer to the International Myeloma Working Group (IMWG) 2016 myeloma response criteria (Appendix 2) and MRD response criteria (Appendix 3).

Note:

According to the IMWG 2016 criteria, documentation of response requires two consecutive

measurements of the applicable disease parameter (serum M-protein, urine M-protein, or serum FLC), performed at any time (no minimum interval is required, it can be done on the same day); however, to confirm response or progressive disease, two discrete samples are required; testing cannot be based on the splitting of a single sample. Bone marrow and imaging assessment do not need to be confirmed by two assessments. Response assessment will continue beyond relapse from complete response (CR) until disease progression is confirmed.

6.3 Pharmacokinetic Evaluation

6.3.1 Pharmacokinetic evaluation parameters

Pharmacokinetic evaluation parameters are the number of CT103A-expanded CAR T cells and VCN in peripheral blood after cell infusion.

PK parameter calculation is based on the actual time of blood collection. If 2 or more assays are reported for the same sampling time, the mean value is calculated before being used for PK parameter calculation (if applicable), and the PK parameters of CAR-T cells as a percentage of leukocytes and VCN are calculated using the non-atrial model method using WinNonlin® software version 8.0 or higher (C_{max} , T_{max} , AUC_{0-28d} , AUC_{0-90d} , AUC_{0-180d} , and AUC_{0-last}).

Descriptive statistics were summarized and tabulated for PK parameters, and box plots were generated for C_{max} , AUC_{0-28d} , AUC_{0-90d} , AUC_{0-180d} , and AUC_{0-last} , with reference to the PK and PD statistical analysis plan for the required statistics.

6.3.2 Pharmacokinetic Blood Sample Collection

It is recommended that the study staffs collect PK blood samples at the timepoints in Table 3 until the dropout visit or the EOS visit.

Table 3 PK Blood Collection Timepoints

PK collection	Planned time	Timepoints	Window
Pre-infusion	NA	1	Baseline
Cell infusion	08:00	No sample collection	-
D1	08:10	2	± 1h
D4	08:10	3	± 3h
D7	08:10	4	± 12h
D10	08:10	5	± 12h
D14	08:10	6	± 12h
D21	08:10	7	± 2d
D28	08:10	8	± 2d
D60	08:10	9	± 14d
D90	08:10	10	± 14d
D180	08:10	11	± 14d
D270	08:10	12	± 14d

PK collection	Planned time	Timepoints	Window
D360	08:10	13	± 14d
D450	08:10	14	± 14d
D540	08:10	15	± 14d
D630	08:10	16	± 14d
D720	08:10	17	± 14d

Note: The test was performed every 6 months ($\pm$ 28 days) at the 5-year post-cell infusion follow-up, regardless of whether the test value was below the lower limit of detection; the test was performed every 12 months at the 5 to 15-year post-cell infusion follow-up until study completion or early withdrawal from the study, or 2 consecutive tests below the lower limit of detection, whichever occurred first; if the last 2 VCN tests within 4-5 years post-cell infusion were below the lower limit of detection, the VCN test was not required at the 5 to 15-year post-cell infusion follow-up.

6.3.3 Pharmacokinetic Blood Sample Handling

Blood specimens should be handled, stored, and transported according to the central laboratory manual.

6.3.4 Pharmacokinetic Blood Sample Testing

After all collected specimens have been sent to the sponsor's designated central laboratory, the central laboratory will perform pharmacokinetic testing using validated methods.

6.4 Pharmacokinetic Evaluation

6.4.1 Pharmacokinetic Assessment Indicators

The amount of peripheral free BCMA.

6.4.2 Blood samples for pharmacokinetic evaluation

The samples of free BCMA in peripheral blood is collected at the same time as the PK blood collection in Table 3 of Section 6.3.2. If the PK blood collection is stopped at the follow-up visit because no BCMA CAR-T cells are detected, the peripheral blood free BCMA collection is also stopped.

6.4.3 Pharmacokinetic Blood Sample Processing

Blood samples should be handled, stored, and transferred according to the central laboratory regulations.

6.4.4 Pharmacokinetic Blood Sample Testing

After all collected samples have been sent to the central laboratory designated by the sponsor, the central laboratory will perform pharmacokinetic testing using validated methods.

6.5 Immunogenicity

Endpoints include: human anti-CAR antibodies.

Immunogenicity will be analyzed throughout the study, including the rate of positivity for human anti-CAR antibodies, antibody levels, and the occurrence of neutralizing antibodies. Blood samples will be collected at the following times: baseline, 28d, 3m, 6m, 12m, 24m, or until the dropout visit.

Processing, storage, and transfer of blood samples should be performed according to central laboratory manual.

The laboratory will perform immunogenicity testing using validated methods.

6.6 RCL

Whole blood will be collected from subjects during the study for RCL testing. The blood collection timepoints in the primary follow-up periods are as follows: baseline, 3m, 6m, 12m, 24m, until the dropout visit. In case of adverse events suspected to be related to RCL during the long-term follow-up, RCL testing should be performed, and follow up to 15 years is required for long-term surviving patients.

Blood specimens should be handled, stored, and transferred according to the central laboratory manual.

The laboratory will use validated methods for RCL testing.

6.7 Inflammatory Factor

Inflammatory factor tests should include at least IL-6, CRP, and ferritin at baseline, -1d, 1d, 4d, 7d, 10d, 14d, 21d, 28d, 2m (60d), 3m (90d), and dropout visit (if the visit is within 2 years post-infusion).

6.8 Detection of Lentiviral Genomic Integration Site

The time points for lentiviral genomic integration site assay in the primary follow-up period are baseline, 14d, 28d, 3m (90d), 6m, 12m, 24m until dropout visit or study completion, whichever occur first. Tests are not required if the VCN value is below the lower limit of detection. The frequency of testing will be synchronized with VCN testing during the long-term follow-up period, and tests are not required if the VCN value is below the lower limit of detection.

The risk of genomic integration of this product during the study must be addressed, and the impact of lentiviral vector integration into the genome of BCMA CAR-T cells should be analyzed (e.g., whether there is clonal growth, whether there is a dominant clone, whether clonal growth leads to malignancy, etc.). The sensitivity, specificity and reproducibility of the assay should be validated, and appropriate positive and negative controls should be designed. If clonal growth of vector-positive cells occurs, or if the test reveals gene integration sites near oncogenes or cancer-associated genes, the testing interval should be shortened to no more than 3 months, and signs of malignancy should be closely monitored until no VCN is detected or until the risk of malignancy is excluded.

7. Adverse Events and Serious Adverse Events

7.1 Definition of Adverse Events (AE)

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Characterization of AEs includes severity, relationship to study drug, day of onset, and outcome. Any event that is new in onset or worsened in severity or frequency from the baseline condition or abnormal results of diagnostic procedures, including laboratory test abnormalities will be considered as an AE.

The following are not considered to be adverse events

- Surgical procedures (e.g., surgery, endoscopy, tooth extraction, infusion). The condition leading to these procedures should be reported as an AE;
- Diseases or conditions that were present or detected during the screening period without subsequent exacerbation, including abnormal laboratory test results;
- The expected progression of the disease. If progression is more severe or occurs more frequently than expected, it should be reported as an AE.

7.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any of the following untoward medical occurrence that at any dose:

1. Result in death.
2. Life-threatening: refers to an event in which the subject 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.
3. Result in hospitalization or prolongation of hospitalization:
 - Generally speaking, hospitalization refers to that the subject is required to be observed and/or treated in a hospital or emergency ward (usually at least over one night).
 - A complication that occurs during hospitalization is considered an AE. If a complication prolongs hospitalization or fulfills the criteria of any other seriousness, the event is an SAE.
 - When it is uncertain whether an AE that occurs in the subject requires “hospitalization” or not, the AE should also be considered an SAE.
 - Hospitalization for elective treatment or due to pre-existing conditions that is not worse than baseline condition is not an AE.

The following hospitalizations are not considered as SAEs:

- Hospitalization for respite care, for example, the disease itself is apart from the criteria for hospitalization, but the subject is hospitalized for respite care.
 - Hospitalization for social reasons, for example, for convenience of care.
 - Planned hospitalization required by the study protocol, for example, hospitalization for use of the investigational drug or laboratory tests required by the protocol.
 - Hospitalization, elective surgery, or test for pre-existing disease planned prior to the informed consent (in this case, the condition requiring hospitalization has not become worse or developed into a new disease after the use of the investigational drug need to be confirmed, with available source document for filing).
 - Hospitalization for routine maintenance (e.g., battery replacement) of device that has been implanted prior to participation in the study.
4. Results in permanent or significant disability or incapacity:
- The term disability refers to the significant impairment of an individual's ability to perform normal life functions. This definition excludes events of relatively minor clinical significance, such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., ankle sprain), which may affect daily life but have not resulted in significant incapacity.
5. Results in congenital abnormality or birth defect in offspring.
6. Other medically significant events:

In some cases, the decision on whether to expedite the reporting must be made based on medical and scientific judgments. For example, a medically significant event is not immediately life threatening, or result in death, or requires hospitalization but might require medical intervention to prevent one of the above outcomes. It is usually considered serious.

7.3 Adverse Drug Reaction (ADR)

ADR refers to any adverse event that occurs in a clinical trial that may be related to the investigational product or treatment. There is at least a reasonable probability of a causal relationship between the investigational product or treatment and the adverse event, i.e., an association cannot be ruled out.

7.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Refers to suspected and unexpected serious adverse reactions whose nature and seriousness of clinical manifestations are beyond the available information such as the investigator's brochure of the investigational drug, the package insert of the marketed drug product, or the summary of product characteristics and is at least possibly related to the treatment.

7.5 Collection and Recording of Adverse Events

7.5.1 Start of AE/SAE collection and recording

All AEs/SAEs are recorded since ICF signing. The results during the screening period will not be recorded as AEs, unless caused by study procedures.

7.5.2 Endpoints for AE/SAE Collection and Recording

- All AEs/SAEs will be recorded until subjects have completed the dropout/withdrawal visit or until 2 years after cell infusion (whichever occurs first). If the withdrawal from the study occurs within 6 months after CT103A cell infusion, efforts should be made to collect AEs until 6 months after the cell infusion provided that the subject cooperates in the collection.
- IP-related AEs/SAEs occurs after dropout visit or 2 years after cell infusion should also be collected.
- SAEs for malignancy, neurological, immunogenic or autoimmune diseases, and infections within 5 years after cell infusion will be collected regardless of association with the IP.

7.5.3 Recording of Adverse Events

During the study, subjects are encouraged to report any AEs, and trained staff will regularly ask the subjects for any AEs in a non-inductive manner. The investigator is to report all directly observed AEs or those spontaneously reported by the subjects in a simple language.

The investigator must use medical terminology and avoid colloquialisms and abbreviations when recording adverse events (AEs). If a diagnosis is available, it should be recorded as the AE instead of individual signs and symptoms. However, if a diagnosis is not available at the time of reporting, each sign and symptom should be recorded. Subsequent diagnoses, if established, should be reported as follow-up information.

In general, adverse events should record the primary event, unless the secondary event is severe (usually $\geq$ grade 3) or a serious adverse event. If the relationship between events is unclear, they should be recorded separately.

If the adverse event persists without remission between assessment time points, it should be recorded as one event. The initial severity of the event should be recorded and updated to the most severe level if the event worsens. If the adverse event resolves and is stable between the two assessment times, but the same adverse event occurs again, it should be recorded separately.

All AEs that occurred during the study are required to be recorded in the source document, including event term, date of onset and date of resolution, severity of the AE, the investigator's judgment on the relationship between the lymphodepleting pretreatment drug/IP and the event, the actions taken and the outcome of the AE. On the basis of a comprehensive consideration of comorbidities and concomitant medications, the relationship to the IP is to be assessed. CRS and ICANS will be recorded separately

in the same manner as AE. Abnormal inflammatory factors associated with CRS will not be recorded as AEs.

In addition, the following elements will be collected for an SAE: SAE onset date (the date of AE changing to SAE), the date when the investigator is aware of AE changing to SAE, SAE criteria, admission and discharge dates (if applicable), assessment of causal relationship between the SAE and study procedures, description of event, etc. For AE with outcome as death, the possible cause of death, death date and autopsy results will also be collected.

7.6 Adverse Event Evaluation

7.6.1 Grading of Adverse Events

Except for CRS and ICANS, adverse events should be graded according to National Cancer Institute Common Terminology Criteria CTCAE Version 5.0 dated 27 November 2017. The grading of CRS and ICANS will be recorded according to the ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells published by ASTCT in 2019 (Appendix 4).

7.6.2 Causality with the Investigational Product

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Unrelated:** The drug was not administered, or the timing of administration and the adverse event did not correlate, or there was another clear cause of the adverse event.
- **Unlikely Related:** The adverse event does not correlate closely with the time of administration, the clinical manifestations are not consistent with the known adverse effects of the drug, and the development of the original disease may also have similar clinical manifestations.
- **Possibly Related:** Drug use is closely related to the time of the adverse event, although supported by the literature; however, more than one drug triggered the adverse event, or the factor of progression of the original disease cannot be excluded.
- **Probably Related:** No history of repeated drug use, the rest of the same "definitely related", or although there is a combination of drugs, but basically can exclude the possibility of combined drug use leading to adverse reactions.
- **Definitely Related:** There is a reasonable temporal relationship between the test drug or treatment and the occurrence of the adverse event; the reaction disappears or rapidly decreases and improves after discontinuation of the drug (i.e., exacerbation positive); the adverse event recurs with the drug (i.e., exacerbation positive) and may be significantly worsened; supported by the investigator's manual or literature; and other confounding factors such as the original disease have been excluded.

If the investigator is unable to make an assessment of the relationship between the adverse event and the study drug, the adverse event should also be considered possibly related to the study drug or treatment.

7.6.3 Expectedness Assessment of Adverse Events

The investigator's brochure serves as the primary document to provide safety reference information for judging whether a serious adverse reaction is expected or unexpected during clinical study. Unexpected adverse reactions refer to that the nature, severity, seriousness, outcome or frequency of the adverse reaction are different from the expected risks described in current safety reference information (i.e., investigator's brochure).

7.7 SAE report

If an SAE is known during the clinical trial, whether or not it is related to the investigational product, the investigator should actively take appropriate measures to ensure the safety of the subject. The investigator should complete the Safety Information Collection Form, sign and date it, and report it to the sponsor (e-mail address: PV@iasobio.com) within 24 hours of awareness of the SAE.

The investigator should follow up on SAEs as required by the protocol and submit a detailed written follow-up report within 24 hours of awareness of the follow-up information in the same manner as described above.

The sponsor or its representative will evaluate and report SAEs in clinical trials in accordance with the latest applicable regulatory requirements for clinical trials.

The investigator must report SUSAR to the institution and the ethics committee promptly after receipt of the sponsor's report.

7.8 Follow-up of Adverse Events

The investigator should follow each adverse event. All SAEs and AEs that was not resolved should be followed until:

- The event is stabilized, resolved or returns to baseline;
- No further improvement will be achieved as determined by the investigator;
- The subject has started a new regimen for the treatment of the study disease;
- When it is impossible to obtain more information (subject died, or the subject refused to provide more information, or there is evidence that the subject has been lost to follow-up).

The recovery time (date) of the adverse event should be recorded in the source document during the trial for the purpose of verifying the raw data.

For serious adverse events, adverse events of special interest, and pregnancy events, the sponsor or other designated personnel may obtain additional information from the subject by telephone, fax, e-mail, and/or observation for the purpose of a more complete medical evaluation of these reported cases.

7.9 Outcomes of Adverse Events

The investigator should determine the outcome of the adverse event based on the status . The outcome of an adverse event includes the following:

- Resolved: The subject has completely recovered f without any residual impact or injury.
- Resolved to Baseline: The values or disease levels return to the baseline before cell infusion.
- Recovering: Signs and symptoms associated with the event have been relieved but have not completely disappeared.
- Resolved with sequelae: The subject has recovered, but with residual impact or injury. These residual impacts may be temporary but persist at the time of reporting. If sequelae are not considered permanent, updated information is required to be additionally provided at the follow-up if there is any change in the event.
- Persistence: Signs and symptoms associated with the event did not decrease and the subject's condition remained unchanged; if the patient died from an AE other than this one, the AE was persistent.
- Worsening: Signs and symptoms associated with the event did not decrease and the subject's condition worsened.
- Death: “Death” is selected as the outcome only for SAEs that resulted in death.
- Uncertain: When the subject is lost to follow-up and the study personnel are unable to determine the outcome.

7.10 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality (if applicable):

- result in discontinuation from the study.
- requires treatment, modification/ interruption of CT103A dose, or any other therapeutic intervention; or
- is judged to be significantly important, e.g. one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criteria need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as AEs. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as an AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result. (eg, record anemia rather than hemoglobin decrease).

7.11 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) include: Grade ≥ 3 Cytopenia (defined as neutrophilia, lymphopenia, thrombocytopenia, and anemia) that persist for more than 30 days, grade ≥ 3 hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), positive anti-CAR antibody, uncontrolled CAR-T cell expansion, tumor lysis syndrome, grade ≥ 3 infection, grade ≥ 3 CRS, grade ≥ 3 ICANS, progressive multifocal leukoencephalopathy, secondary malignancy, RCL.

If the AESI meets the SAE criteria, it is required to be handled according to SAE reporting procedures detailed in Section 7.7.

7.12 Disease Progression

Disease progression refers to the worsening of a subject's condition caused by the disease being treated with the IP. It may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease. Disease progression in this study will be assessed according to the IMWG 2016 criteria. Events determined to be caused by disease progression during the study should not be reported as AEs or SAEs.

For death that is determined as caused by disease progression, the death date and cause of death should be recorded in the eCRF, and the death should not be reported as an SAE.

7.13 New Cancers

New cancers should be considered as SAEs. New primary cancers are those that are not the primary reason for the study treatment and are discovered after the subjects are enrolled in the study.

8. Pregnancy

To ensure the safety of subjects, if the female subject or the female partner of the male subject becomes pregnant during the study treatment or within 2 years after the study treatment, the Pregnancy Report Form is required to be filled in and reported to the sponsor within 24 hours after the investigator is aware of the pregnancy. Also, the pregnancy must be followed up to determine the outcome (if the male subject's female partner gives consent to information collection), including spontaneous or induced abortion, details of the birth, congenital malformations, or maternal or newborn complications, which are to be reported using a Pregnancy Report Form.

Reports of spontaneous abortion, ectopic pregnancy, induced abortion due to medical and health reasons, fetal death, neonatal SAE (not limited to neonatal death, all congenital malformations/birth defects) are considered serious adverse events (SAEs). In addition to the completion and reporting of the Pregnancy Report Form, it is also necessary to report the SAE and complete the Safety Information Collection Form. Elective abortion without complications is not considered an adverse event. If other SAEs occur during pregnancy, the Safety Information Collection Form must also be completed, and the SAE must be reported.

9. Data Processing

The data management in this study will be conducted in accordance with relevant national laws and regulations.

9.1 Data Collection

An electronic data capture (EDC) system will be used in this study, and study data (except for pharmacokinetics and immunogenicity) will be entered into eCRF by the investigator or authorized study site personnel. The investigator and authorized study site personnel will be properly trained prior to the initiation of the study site or the data entry, and appropriate information safety actions will be taken.

All data will be entered in Chinese. The eCRF should be completed as soon as possible during or after the visit and be updated at any time to ensure that the latest development of the subject involved in the study is reflected. To avoid differences in the results of assessments by different investigators, it should be ensured that the baseline and all subsequent efficacy and safety assessments for the same subject will be completed by the same individual. The investigator will review data to ensure the accuracy and correctness of all data entered into the eCRF. If some assessments are not done during the study, or if some information is unavailable, inapplicable, or unknown, the investigator will record them on the eCRF. The investigator will electronically sign the verified data.

Unless otherwise specified, eCRF will only be used as a form for collecting data, not as raw data. Source documents refer to all records used by investigators or study sites, related to subjects, and that serve as evidence of existence of the subjects, inclusion/exclusion criteria and their participation in the study, including laboratory records, ECG results, subject's file, etc.

The investigator is responsible for maintaining all source documents and ensures to be monitored by clinical research associate (CRA) at each visit. In addition, the investigator should submit a complete eCRF for each subject involved in the study regardless of the duration of the subject's participation in the study. All supporting documentation (such as laboratory or site records) submitted together with the eCRF should be carefully verified for study number and subject number, and all private personal information (including the subject's name) should be deleted or made illegible to protect the subject's privacy.

When study data is entered into eCRF, the system will automatically add the identity of the data entry personnel through the ID of the user who has logged in. The investigator certifies that he/she has reviewed the record by electronically signing the record and ensures the accuracy of the data in the record. The electronic signature will be done using the investigator's user ID and password, and the system will automatically show the date and time of the electronic signature. Any change to the data in the eCRF should follow the workflow defined by the EDC system. All changes and their reasons will be recorded in the audit trail.

9.2 Data Monitoring

The CRA will review the source document and eCRF and assess their completeness and consistency. The CRA will also compare the eCRF with the source document and other relevant documents to ensure the integrity and consistency of core data.

9.3 Data Entry and Modification

All data entries, corrections, and modifications will be the responsibility of the investigator or his/her authorized personnel. The monitor has no access. The data in the eCRF is submitted to the data server, and any changes to the data will be recorded in the audit trail, that is, the reason for the change, the name of the operator, the time and date of the modification will be recorded. The role and permission of the staff responsible for data entry at the site will be predetermined. If there is a data challenge, the CRA or data management personnel will issue a challenge in the EDC, and the site staff will be responsible for answering the question. The EDC system will record the audit trail of the challenge, including the investigator's name, time and date.

9.4 Data Lock

The data set population will be determined jointly by the investigator, sponsor, the statistical analysis lead, and data management lead and other project related personnel (if needed), and then the data manager will lock the database.

9.5 Data transfer

After the database is locked, the statistical analysis personnel will conduct statistical analysis according to the requirements of the Statistical Analysis Plan (SAP). After the statistical analysis is completed, the medical writer is responsible for the clinical study report.

10. Statistical Analysis

Further technical details (e.g., missing value handling) will be provided in the SAP. Any discrepancy between the SAP and the protocol will only be listed, described, and explained in the SAP, except for changes in the primary study endpoint and the primary analysis method, which are required to be concurrently reflected in the protocol.

10.1 Sample Size

Phase I clinical trials were designed to enroll 6-20 subjects, and enrollment was completed in this phase with a total of 17 subjects.

According to preliminary research, the ORR of drugs approved for marketing or in clinical trials are less than 35% (Table 4); except for pomalidomide in the NDA process, all others are not approved on the marketing in China. Based on the above considerations, the ORR of phase II was proposed to be 35% as the threshold for sample size calculation.

Table 4 Summary of ORR Data for Selected Drugs in the RRMM Population

Drug Name	Proposed Indication:	Median lines (Range)	Status in the US	Status in China	ORR	References
Single-Agent						
Satuximab	RRMM, ≥ 3 lines or refractory to both a proteasome inhibitor and an immunomodulatory agent	5 (2-14)	Phase III	Phase III	24%	¹³
Carfilzomib	RRMM	5 (1-20)	On marketing	Phase III	28%	¹⁴
Pomalidomide	RRMM	5 (1-17)	On marketing	NDA	19%	¹⁴
Elotuzumab	RRMM	4.5 (2-10)	On marketing	/	0	¹⁵
Daratumumab	RRMM, ≥ 3 lines or refractory to both a proteasome inhibitor and an immunomodulatory agent	5 (2-14)	On marketing	Phase III	29.2% (16mg/kg)	¹⁶
dual-agent treatment						
Pomalidomide plus low-dose dexamethasone	Refractory to proteasome inhibitor and immunomodulatory agent	/	/	/	28%	¹⁷

In the non-registered clinical trials of this product, a 3-month ORR of 77.8% (7/9) was observed in the RP2D intent-to-treat population; other CAR-T clinical trials with the same BCMA target have reported ORRs ranging from 60% to 100%.

Therefore, hypothesis at the confirmatory study phase was performed based on whether the ORR was greater than 35%, i.e., $H_0: p \leq 0.35$ vs. $H_1: p > 0.35$. Therefore, assuming the 3-month ORR is 60% in the full analysis set (FAS), with a one-sided $\alpha = 0.025$, at least 53 subjects in the FAS are required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis. In this stage, 78 subjects have received

cell infusion. The hypothesis test of the bridging study is based on whether the ORR at 3 months is greater than 35% (i.e., $H_0: p \leq 0.35$ vs $H_1: p > 0.35$). Combined with the results of the confirmatory study, the 3-month ORR in the FAS is expected to be 80% with a one-sided $\alpha = 0.025$. Therefore, a minimum of 14 subjects in the FAS population is required to have at least 95% power to reject the null hypothesis and accept the alternative hypothesis.

In summary, at least 109 subjects are required to complete the CT103A infusion in this study. However, considering a 10% drop-out rate between enrollment and infusion, it is expected that a total of 120 to 125 subjects meeting the inclusion criteria are expected to be enrolled.

10.2 General Principles of Statistical Analysis

PK parameter calculations will be performed using WinNonlin 8.0 or higher, and all the other statistical analyses will be performed using SAS® 9.4 or higher.

Unless otherwise specified, the summary table will be provided at planned timepoints for the study. Unplanned timepoints are generally only displayed in listings, and the listings will be categorized by variables such as subject number and assessment timepoints. For continuous variables (e.g., age), descriptive statistics of the number of observations, mean, median, quartile, standard deviation, minimum, and maximum will be presented; for categorical variables, descriptive statistics of the number and percentage for each category will be presented; geometric mean and geometric coefficient of variation will also be calculated for PK parameters such as AUC and C_{max} . The median time and its 95% confidence interval will be estimated for time-to-event data using the Kaplan-Meier method. The decimal places of the minimum and maximum are consistent with those recorded in the CRF. The mean and median are reported to 1 more decimal place than the raw data, the standard deviation is reported to 2 more decimal places than the raw data, and the percentage is rounded up to 2 decimal places. All statistics are generally rounded up to no more than 4 decimal places.

With the exception of subject disposition, other statistical summary tables and graphs will be based on corresponding analysis sets, and all subjects will be presented in listings.

For detailed statistical analysis methods, please refer to the Statistical Analysis Plan (SAP).

10.3 Handling of Missing Values

Efficacy indicators: All primary efficacy indicators missing due to early withdrawal were analyzed as "No response". Censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively.

Unless otherwise specified, missing values of baseline data, safety data, pharmacokinetic data, and exploration endpoint data will not be imputed.

For extreme values of laboratory data caused by improper handling of specimens and blood samples, the data of corresponding unscheduled visits will be used for the analysis or that they will be excluded from the analysis as missing values.

10.4 Analysis Population

Primary statistical analysis sets are as follows:

- Screened analysis set: All subjects who have signed the informed consent form will be included in the screened analysis set.
- Enrolled analysis set (EAS): Subjects in the screened analysis set who meet the inclusion criteria but do not meet the exclusion criteria and who have been assigned an enrollment number will be included in the EAS.
- Apheresis analysis set: Subjects in the enrolled analysis set from whom the mononuclear cells have been collected will be included in this analysis set.
- Lymphodepleting pretreatment analysis set: Subjects in the enrolled analysis set who have received lymphodepleting pretreatment will be included in the lymphodepleting pretreatment analysis set.
- Full Analysis Set (FAS): All subjects who have received CT103A infusion will be included in this analysis set. FAS is the primary analysis set for efficacy endpoints.
- Per-Protocol Analysis Set (PPS): A subset of FAS, including all subjects in FAS without missing efficacy assessment measurements and without major protocol deviations that affect the efficacy. The PPS analysis of efficacy endpoints will be considered supportive.
- Safety Set (SS): All subjects who have received cell infusion and have at least one post-treatment safety assessment will constitute the safety analysis set of this study. The SS will be used for the analysis of safety measurements.
- Pharmacokinetic Analysis Set (PKS): All subjects who have received the study treatment and have at least one post-treatment PK assessment data (concentration/parameter) will constitute the PK analysis set of this study.
- Pharmacodynamics Analysis Set (PDS): All subjects who have received the study treatment and have at least one post-treatment PD assessment data will constitute the PD analysis set of this study.

10.5 Analysis Contents

The values when the subjects are enrolled in the study will be used as demographics and other baseline characteristics as well as the baseline for the analysis of safety measurements; the assessment values during the baseline period before lymphodepleting pretreatment will be used as the baseline for the analysis of efficacy and relevant measurements.

10.5.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, completed, and discontinued during the study, as well as the reasons for all discontinuations will be summarized by treatment group, for all sites combined and each site separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing. Protocol Deviation data will be listed for each patient.

10.5.2 Demographics and Baseline Analysis

Demographics and other baseline characteristics will be summarized and/or analyzed; Continuous variables will be summarized using the number of observations, mean, standard deviation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

10.5.3 Analysis of Safety Measurements

AEs

AEs will be analyzed based on the time of occurrence as listed below: from apheresis to lymphodepleting pretreatment, from the start of lymphodepleting pretreatment to before cell infusion, and after cell infusion, and AEs that occur after cell infusion will be primarily analyzed.

Adverse events (AEs) will be coded according to MedDRA. The number of subjects who experienced AEs and incidence of AEs as well as AEs, SAEs, AESIs after cell infusion will be summarized by SOC and PT, and a listing of relevant AEs will be provided. In addition, the severity of AEs after cell infusion will be presented according to NCI CTCAE Version 5.0 by SOC and PT.

CRS and ICANS will be summarized and/or analyzed by the severity grade (2019 ASTCT grading criteria).

Laboratory tests

Clinical laboratory values will be graded according to CTCAE version 5.0 for applicable tests. If the CTCAE grade cannot be judged, the results will be judged as “Low”, “Normal” and “High” according to the laboratory normal range. Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented for selected lab test at each scheduled visit. Frequency distributions for shift from baseline to the worst grade will be presented.

Listings of clinical laboratory data with NCI CTCAE grades (if applicable) and abnormal flags (low or high) will be provided.

Vital signs, Physical examination, ECG, ECOG performance score, Echocardiography, etc.

The data and their changes from baseline will be summarized using descriptive statistics at each visit, and the abnormalities will be presented in a listing using descriptive statistics. For specific statistical analysis methods, please refer to the SAP.

10.5.4 Analysis of Efficacy Measurements

Primary Efficacy Analysis and Hypothesis Testing

In the FAS set of the Phase II trial, 3-month ORR as assessed by the Independent Review Committee (IRC) were calculated and their bilateral 95% confidence intervals (CI) were estimated using the Clopper-Pearson exact method. If the lower 95% CI was greater than 35%, the null hypothesis H0 was rejected and the alternative hypothesis H1 was

acceptable.

Supportive Analysis of Primary Efficacy Endpoint

Data from the Phase I FAS (n1) and the Phase II FAS (n2) were combined for analysis, and 3-month ORR values were calculated based on the IRC assessment. A class I error α of $n1/(n1+n2) \times 0.05$ (bilateral) was assigned to phase I using the conservative Bonferroni method. The remaining α was assigned to the combined phase I/II pooled data and its confidence interval was calculated using the Clopper-Pearson exact probability method.

Supportive Analysis of Secondary Efficacy Endpoints

- Investigator-assessed 3-month ORR: Investigator-assessed 3-month ORR values were calculated by study phase and their bilateral 95% confidence intervals (CI) were estimated using the Clopper-Pearson exact method.
- IRC and investigator-assessed 3-month ORR concordance analysis: The results of the different assessment methods were listed separately using paired rows $\times$ tables, and the number and proportion of discordant results were calculated.
- Best ORR: Estimates of best ORR at 1, 3, and 6 months were calculated by study phase and adjudicator (investigator assessment, IRC assessment), and their two-sided 95% confidence intervals (CI) were estimated using the Clopper-Pearson exact method.
- DOR, PFS and OS: Median DOR, PFS and OS were calculated by study phase and assessment method (investigator assessment, IRC assessment) and their two-sided 95% CIs were estimated using the Brookmeyer and Crowley method, also plotted their Kaplan-Meier survival curves and calculated 6, 12, 18 and 24-month survival rates and their 95% CIs.
- TTR and TTCR: Descriptive statistics were summarized for TTR and TTCR by study phase and assessment method (investigator assessment, IRC assessment). Only subjects who achieved response in the FAS set were analyzed.
- MRD efficacy assessment: The proportion of subjects with MRD negativity detected by flow cytometry and the duration of MRD negativity were calculated by study phase.

10.5.5 PK/PD Analysis

The PK/PD analysis will be based on the PK and PD analysis sets, respectively, and the PK blood sampling schedule and derived deviations in sampling will be provided.

Transgene vector copy number (VCN, copies/ μ g gDNA) and CAR-positive cell counts (cells/ μ L) data at each time point will be summarized using descriptive statistics. Individual concentration-time profiles and arithmetic median concentration-time figures will be plotted in linear and semi-logarithmic forms against scheduled visit. According to the actual blood sampling time, PK parameters will be calculated by non-compartmental model using WinNonlin software.

Main PK parameters: maximum concentration of expanded BCMA CAR-T cells and VCN in peripheral blood after administration (C_{max}), time to reach the maximum concentration (T_{max}), area under the curve from 0 to day 28 (AUC_{0-28d}), area under the curve from 0 to day 90 (AUC_{0-90d}), area under the curve from 0 to day 180 (AUC_{0-180d}), area under the curve from 0 to last (AUC_{0-last}). Descriptive statistical summary analysis was performed for PK parameters based on PK measures (CT103A cell concentration and lentiviral vector copy number, with focus on lentiviral copy number) at different study stages.

PD analysis

Free BCMA assay was performed at different time points of blood collection before and after cell infusion. Descriptive statistics of free BCMA in peripheral blood from selected visits were summarized according to different study phases and dose groups, and concentration data were tabulated separately according to the efficacy evaluation classification.

Concentrations of CAR T-related inflammatory factors CRP, IL-6, and ferritin and their changes from baseline at each time point were analyzed by descriptive statistics according to study phase, and trends were shown by line graphs. Exploratory analysis of the correlation between inflammatory factors (CRP, IL-6, ferritin) and clinical safety and efficacy will be summarized and analyzed based on CRS levels and IMWG efficacy assessment results for the corresponding visit points.

10.5.6 Other Exploratory Variables

Immunogenicity analysis

The presence of human anti-CAR antibodies and the antibody titer will be analyzed and calculated using descriptive statistics. Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects who developed anti-CAR antibodies. The effect of anti-CAR antibodies on pharmacokinetics, safety, and efficacy may also be evaluated if sufficient data are obtained. Details will be specified in Statistical Analysis Plan.

Replication competent lentivirus

By study phases, the proportion of subjects with positive or negative RCL test results will be analyzed using descriptive statistics.

10.6 Interim analysis

After the 53rd subject in the Phase II clinical trial has completed the cell infusion and the 3-month primary efficacy assessment is complete, analysis of key efficacy indicators and statistical extrapolation will be performed for submitting to regulatory authorities.

After completion of safety observations in 100 subjects, a safety summary analysis will be performed and submitted to regulatory authorities for full marketing approval.

10.7 Final Analysis

The final analysis will be performed when the last subject in this study completes 2-year

follow-up after cell infusion, and a descriptive analysis will be conducted on endpoints such as the safety, efficacy, and kinetic characteristics of this product.

11. Independent Review Committee (IRC)

To ensure the objectivity and independence of the evaluation, an independent review committee (IRC) will be established for this study. The IRC will independently evaluate the efficacy data according to the IMWG 2016 standard. The IRC evaluation will not only include imaging data but also the parameters reported by the central laboratory. The specific workflow and content are described in the IRC charter.

12. Data Monitoring Committee (DMC)

In order to utilize safety and efficacy data and conduct a risk-benefit assessment of this study, the sponsor will establish an independent Data Monitoring Committee (DMC) prior to the first subject's cell infusion in Phase II.

The responsibilities and tasks of the DMC mainly include periodic or unplanned review of efficacy and safety data during the study, providing recommendations to the sponsor based on the risk/benefit assessment.

The DMC charter for this study will clearly define the composition of members and their job responsibilities, including:

- Review and approve the DMC charter;
- Review the results of the interim data analysis;
- The DMC statistical expert will review the interim analysis plan and provide interpretation of the data analysis results;
- Review individual events that are considered significant by the clinical experts;
- Address other issues of concern to the study team but should not imply summary information/conclusions on safety or efficacy.
- The DMC is responsible for alerting the sponsor to potential safety issues and, in addition, for making recommendations regarding the progress of the trial that are of concern to the sponsor, including changes to the informed consent form;
- The DMC is responsible for reviewing the results of all formal interim analyses and making recommendations to the sponsor;
- The DMC will make recommendations and vote on the continuation of the trial at the DMC meeting;
- Review the meeting minutes of the DMC meeting and make recommendations on how to proceed with the trial.

Documents related to the work of the DMC (meeting agendas, minutes, DMC statistical analysis plans, programmed statistical output forms, graphs and tables of data, DMC meeting proposals, quality control lists, document lists, DMC member signature pages, correspondence, etc.) will be collected and managed centrally by the independent statistical team and submitted to the sponsor after the database is closed for New Drug Application. Once the DMC-related documents are submitted to the sponsor, the independent statistical team will retain the electronic documents related to the DMC's work. For clinical trials that are used for new drug applications, the electronic files related to the DMC work will be kept until 5 years after the investigational product is approved for marketing; for clinical trials that are not used for new drug applications, the electronic files related to the DMC work will be kept until 5 years after the clinical trial is completed.

13. Clinical study report (CSR)

The CSR will be completed in accordance with GCP and corresponding guidance.

14. New Drug Application Plan

The original plan was to submit a conditional marketing application to the CDE when the efficacy endpoint of the pivotal Phase II trial was met (3-month ORR in approximately 53 subjects) and to simultaneously submit the 3-month ORR in Phase I/II (approximately 70 subjects in total) as supporting data for the trial. After communication with the CDE, the CDE proposed to submit additional subjects with 3-month post-infusion ORR data, so that clinical data for the first 79 subjects (Phase I: 17, Phase II: 62) who received cell infusion through January 21, 2022 (i.e., the date the 79th subject completed the 3-month efficacy assessment and the 70th subject completed the 6-month efficacy assessment) were included.

The CDE requested that a Phase II bridging study be conducted to confirm the clinical efficacy and safety of the investigational product after the change in manufacturing site. Therefore, the study will continue with a bridging study of at least 14 subjects receiving CT103A infusion prepared at the new manufacturing site concurrently with the conditional marketing application and is expected to complete a total of approximately 109 subjects with efficacy and safety observations prior to submitting a full marketing application to the CDE.

15. Data Storage

During the study and after the study is completed, the study site/sponsor will file the necessary documents in the study documentation file in accordance with the requirements of Chinese GCP.

In addition, these documents will be maintained until

- At least 5 years after the completion or early termination of the trial; or
- At least 5 years after final approval of the marketing application in China and until there are no more marketing applications pending or under review in China; or
- At least 5 years after the formal termination of the clinical development program for the investigational product.

whichever is longer.

The sponsor should promptly notify the investigator of any documents that are no longer required. These documents should not be destroyed/removed without first informing the sponsor and obtaining its consent.

16. Informed Consent Form

Subjects will be informed orally and in writing by the investigator of the nature, purpose, and risks of the screening procedures, as well as the study objectives, procedures, limitations, obligations, benefits, risks, rewards, insurance coverage, and possible adverse drug reactions, prior to initiating the screening procedures. Before each subject is enrolled in the clinical study, the written informed consent form, and the process of signing the informed consent form will be obtained. The subject information and the informed consent form must be signed and dated. The informed consent form is in duplicate, one copy is kept by the subject, and the investigator retains one original as part of the clinical study records. The investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The time of obtaining the informed consent form must be recorded in the EDC system. The informed consent form must be kept in the investigator file.

If amendments to the study protocol are required, the subject information and the informed consent form may require amendments to reflect the changes in the study protocol. Any amendments to the subject information and the informed consent form must be submitted to independent ethics committee (IEC) for review and approval, and all subjects enrolled in the clinical study thereafter and subjects who are currently performing the clinical study follow-up must sign the amended subject information and the informed consent form that have been reviewed and approved by IEC.

The keeping of study results should be consistent with information protection laws in China. Subjects should be informed that the monitors, auditors, ethics committee and inspectors of drug regulatory authorities may access the original medical records of the subjects to verify the process and data of the clinical study under the condition that the principle of confidentiality and relevant regulations are not violated.

The investigator will keep a subject identification code sheet (subject number and corresponding subject's name) to identify corresponding records.

17. Quality Control

17.1 Monitoring

This study will be monitored according to the GCP. Monitoring visits will be performed as required by all relevant laws and regulations. The capabilities of each study site, the facilities, and technical equipment required to conduct the study will be assessed. From subject enrollment, monitoring visits will be regularly performed at each study site. Also, the data entered into the eCRF will be compared with the raw data, and the investigator will be informed of errors or omissions. The study site's compliance with the study protocol will also be ensured, the supply of IPs will be arranged, and it will be ensured that the drug products are stored under appropriate conditions.

17.2 Data Verification

It is required in this study that the monitor should have direct access to the raw data for verification, which is achieved by reconciling the data on the subject's eCRF with the data in the source document. This data verification process is an important part to ensure the quality of the study, and entry errors and omissions can be changed in this process.

17.3 Audits and Inspections

The sponsor's representative, regulatory department, and independent ethics committee may perform the audit or inspection at the site, including raw data verification.

17.4 Personnel Training

The principal investigator will keep an authorized assignment sheet and training record of all study-related personnel. It will be ensured that all these personnel have been properly trained and authorized in relation to the study and that any information associated with the conduct of the study has been transmitted to relevant personnel.

18. Approval of Study Protocol and Amendments

Before initiating a clinical study, the study protocol and other relevant documents of the clinical study will be submitted to the IEC/competent authority for approval according to local legal requirements. The sponsor and the investigator must ensure that all ethical and legal requirements are met prior to the enrollment of the first subject in the clinical study.

The study protocol must be strictly followed during the study. Changes to the study protocol require written amendments, which will be issued by the responsible personnel and approved by the IEC/competent authority (if applicable) prior to implementation.

19. Study duration

This study is divided into a primary follow-up period and a long-term follow-up period. The main follow-up period is from the first day to 2 years after cell infusion.

This study started in 2019, and the primary follow-up period is assumed to last for 4-5 years. The long-term follow-up period is from the completion of the main follow-up period to 15 years after cell reinfusion.

20. Protection of Confidential Data

All the clinical study results and documents will be maintained confidential. Such information is not to be disclosed by the investigator nor members of the study team without the prior approval of the sponsor.

The identities of the subjects involved in the study shall not be disclosed. Subjects may only be represented by the subject number, initials, or date of birth in eCRF and other documents, and the subject's name shall not appear. The investigator must maintain documents confidential, where the subject (e.g., the subject information and the informed consent form that have been signed) identity is indicated.

21. Liability and Insurance

The insurance coverage will be set up in accordance with GCP guidelines and relevant local insurance laws, and subjects will be indemnified in the event of death or any damage to the subject's health or living conditions as a result of participation in the study.

22. Publication Policy

The sponsor reserves the right to review the initial draft prior to the publication or release of the study results.

All information and results obtained from this study, as well as all intellectual property rights, are owned by the sponsor, and the sponsor may utilize the information in various forms, such as submitting it to governmental drug regulatory authorities or disclosing it to other investigators.

At the same time, the study personnel may use data obtained from this study alone for scientific purposes but must consult with and obtain the written consent from the sponsor prior to the publication. The sponsor recognizes that the investigator has the right to publish the study results after the study is completed. However, the study personnel must send a draft or abstract of the article to the sponsor 30 days before the submission so as to obtain the approval by the sponsor before posting the final version of the article to be published. The sponsor will review the article in a timely manner and will not unduly withhold the approval. When there is a discrepancy between the sponsor and the investigator, the content to be published should be discussed in order to reach a mutually satisfactory solution.

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24. Appendix

24.1 Appendix 1 ECOG Performance Status

Table 5 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature
2	Ambulatory and capable of all selfcare but unable to carry out any work activities, not confined to bed up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Totally confined to bed, cannot carry on any selfcare
5	Dead

Reference:

Ken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

24.2 Appendix 2 Response Assessment of Multiple Myeloma-Revised IMWG Criteria

Table 6 Standard IMWG response criteria¹

Response Category	Response criteria
Stringent complete response (sCR)	Complete response as defined below plus normal FLC ratio ² and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ patients, respectively, after counting ≥ 100 plasma cells) ³
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $< 5\%$ plasma cells in bone marrow aspirates
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
Partial response (PR)	$\geq 50\%$ reduction of serum M-protein plus reduction in 24 h urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was $\geq 30\%$; In addition to these criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD)⁴ of soft tissue plasmacytomas is also required.
Minimal response (MR)	$\geq 25\%$ but $\leq 49\%$ reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) ⁴ of soft tissue plasmacytomas is also required.
Stable disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease ^{5,6}	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: ➤ Serum M-protein (absolute increase must be ≥ 0.5 g/dL); ➤ Urine M-protein (absolute increase must be ≥ 200 mg/24 h); ➤ In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); ➤ In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be $\geq 10\%$); • Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL

Response Category	Response criteria
	• Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD of > 1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion > 1 cm in short axis; • $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD of the measurable lesion; • Hypercalcemia (> 11 mg/dL); • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein.
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis⁷; • Development of $\geq 5\%$ plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)

Note:

IMWG = International Myeloma Working Group. FLC = free light chain. M-protein = myeloma protein. SPD = sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions.

1. Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a $\geq 90\%$ decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

2. All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
3. Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of $> 4:1$ or $< 1:2$.
4. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.
5. Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.
6. In the case where a value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.
7. Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

Reference:

Kumar, Shaji, et al. "International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma." *The lancet oncology* 17.8 (2016): e328-e346.

24.3 Appendix 3 Response Assessment of Multiple Myeloma-MRD Response Criteria

Table 7 IMWG MRD criteria (requires a complete response as defined below)

Response Category	Response Criterion ¹
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years) ²
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF ³ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells ⁴ or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue ⁵ .
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of $\geq 5\%$ clonal plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Note:

IMWG = International Myeloma Working Group. MRD = minimal residual disease. NGF = next-generation flow. NGS = next-generation sequencing. M-protein = myeloma protein. FCM = flow cytometry. SUVmax = maximum standardized uptake value. MFC = multiparameter flow cytometry. ¹⁸F-FDG PET = ¹⁸F-fluorodeoxyglucose PET. ASCT = autologous stem cell transplantation.

1. All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response.
All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.
2. Sustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative).

3. Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.
4. DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequentia).
5. Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax = 2.5 within osteolytic CT areas > 1 cm in size, or SUVmax = 1.5 within osteolytic CT areas $\leq$ 1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

Reference:

Kumar, Shaji, et al. "International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma." *The lancet oncology* 17.8 (2016): e328-e346.

24.4 Appendix 4 Guidelines for Management of Adverse Reactions

According to the preliminary clinical data of CT103A and integrating the reports of adverse reactions of similar products, the adverse reactions related to BCMA CAR-T treatment mainly include: cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections (bacteria, fungi, viruses), viral reactivation, grade ≥ 3 organ toxicity (such as hematological toxicity, abnormal coagulation function, hypogammaglobulinemia), fulminant hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), tumor lysis syndrome (TLS), replication competent lentivirus, uncontrolled T cell proliferation, tumorigenic risk, acute infusion reactions or adverse reactions to excipients.

This appendix is only for the reference of investigators in clinical studies and is not a mandatory document.

24.4.1 Cytokine Release Syndrome (CRS)

(1) Definition and clinical manifestations

CRS is defined as “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.” Syndromes such as fever, nausea, headache, tachycardia, hypotension, rash and impeded breathing induced by the release of inflammatory cytokines such as TNF- α , IL-1, IL-6, IL-12, IFN- α , IFN- β , IFN- γ , MCP-1 and IL-8. It is frequently clinically characterized by systemic symptoms such as fever, asthenia, anorexia and myalgia, and other organs and systems may also be affected, including the cardiovascular system, respiratory system, skin, gastrointestinal tract, liver, kidney, blood system, and nervous system. ([Table 8](#))

Table 8 CRS-related clinical symptoms

CRS-related clinical symptoms include	
1) Complex symptoms	Fever (may be accompanied by rigor), listlessness, lassitude, anorexia, muscle pain, arthralgia, nausea, vomiting, headache
2) Skin	Rash
3) Gastrointestinal	Nausea, vomiting, diarrhea;
4) Respiratory system	Polypnea, hypoxemia
5) Cardiovascular	Tachycardia, pulse pressure increased, hypotension, cardiac output increased (early), cardiac output decreased (advanced);
6) Coagulation	D-dimer increased, hypofibrinogenemia (possibly with bleeding)
7) Kidney	Azotemia;
8) Liver	Transaminases increased, hyperbilirubinemia;
9) Nervous system	Headache, mental status changes, mental aberration, obnubilation, aphasia, hallucination, tremble, dysmetria, gait changes, epilepsy;

CRS-related clinical symptoms include

10) Complications	Complications of CRS with potentially fatal consequences include: cardiac dysfunction, adult respiratory distress syndrome, neurotic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.
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(2) Risk factors

The risks factors of CRS include high tumor burden (> 50% bone marrow blasts), multiple comorbidities, multiple prior chemotherapy cycles and regimens, rapid disease progression after lymphodepleting chemotherapy, active infection or inflammation within 3 days of infusion. Serious events that may be associated with CRS include arrhythmia (including atrial fibrillation and ventricular tachycardia), cardiac arrest, heart failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and HLH/MAS.

(3) Diagnosis and grading

There are currently multiple criteria for CRS grading at home and abroad, and different criteria are used at different centers. The 2019 ASTCT grading of CRS is used as the criteria in this study. In these criteria, CRS is only graded by fever, blood pressure level and oxygen saturation, which is convenient for clinicians to make judgments as soon as possible, treat the condition in time, and maintain good consistency in multiple centers. These grading criteria are recommended for clinical studies and post-marketing products. Grading of CRS is shown in [Table 9](#):

Table 9 Grading of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever ¹	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor (with or without vasopressin)	Requiring multiple vasopressors (with or without vasopressin)
And/or ²				
Hypoxia	None	Requiring low-flow nasal cannula ³ or blow-by	Requiring high-flow nasal cannula ³ , facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

1. Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy (e.g., tocilizumab) or hormone therapy, fever is no longer required to grade subsequent CRS severity, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the most severe event: hypotension or hypoxia not attributable to any other cause. For example: A patient with a temperature of 39.5°C who requires one vasopressor for hypotension, and requires low-flow nasal cannula for hypoxia is classified as grade 3 CRS.

3. Low-flow nasal cannula is 6 L/min, including blow-by (occasionally used in children). High-flow nasal cannula is > 6 L/min.

(4) Treatment

For patients with high suspicion of CRS, early and timely intervention and monitoring assessment should be conducted. The CRS score should be assessed twice a day. The frequency of assessment should be increased if there are changes in the condition.

In general, principles for managing CRS are as follows:

- The severity of CRS should be graded;
- Take different treatment measures depending on the grade of CRS;
- For patients at high risk of severe CRS, regardless of the grade, tocilizumab and glucocorticoids are allowed to be co-administered, and glucocorticoids can be given until symptoms are relieved;
- For serious leak syndrome and cardiac insufficiency, continuous renal replacement therapy (CRRT) and/or plasma exchange are/is effective treatment;
- Vigilance of the possibility of severe comorbid infection is required for CRS.

Table 10 Recommendations on management of CRS¹

CRS Grade ^a	Tocilizumab ^b	Corticosteroid ^b	Other Supportive Care ^b
Grade 1 Fever ($\geq 38^{\circ}\text{C}$) with or without constitutional symptoms	For CRS > 3 days with significant symptoms or comorbidities consider < 30 kg: Administer tocilizumab ^c 12 mg/kg IV over 1 hour ≥ 30 kg: Administer tocilizumab ^c 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose).	Consider dexamethasone 10 mg IV QD for CRS that occurs < 72 hours post-infusion	Sepsis screen; Empiric use of broad-spectrum antibiotics if neutropenia; Maintain intravenous infusion of fluids for hydration; Electrolyte repletion; Symptomatic treatment of organ toxicity.
Grade 2 Fever ($\geq 38^{\circ}\text{C}$) with hypotension not requiring vasopressors and/or hypoxia requiring low flow (≤ 6 L/min) oxygen delivery	< 30 kg: Administer tocilizumab ^c 12 mg/kg IV over 1 hour ≥ 30 kg: Administer tocilizumab ^c 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat in 8 hours if no improvement, no more than 3 doses in 24 hours, maximum of 4 doses total.	For persistent refractory hypotension after 1-2 doses of tocilizumab, consider dexamethasone 10 mg IV Q12-24 hours	IV fluid bolus as needed; For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: start vasopressors, consider transfer to ICU, consider echocardiogram and initiate other methods of hemodynamic monitoring; Manage per Grade 3 if not improvement within 24 hours after starting anti-IL-6 therapy; Symptomatic

CRS Grade ^a	Tocilizumab ^b	Corticosteroid ^b	Other Supportive Care ^b
			management of organ toxicities.
Grade 3 Fever ($\geq 38^{\circ}\text{C}$) with hypotension requiring 1 vasopressor with or without vasopressin and/or hypoxia requiring high flow cannula, face mask, nonrebreather mask, or Venturi mask.	< 30 kg: Administer tocilizumab ^c 12 mg/kg IV over 1 hour ≥ 30 kg: Administer tocilizumab ^c 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat in 8 hours if no improvement, no more than 3 doses in 24 hours, maximum of 4 doses total.	Dexamethasone 10 mg IV Q6 hours. If refractory, manage as Grade 4.	Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring; Supplemental oxygen; IV fluid bolus and vasopressors as needed; Symptomatic management of organ toxicities.
Grade 4 Fever ($\geq 38^{\circ}\text{C}$) with hypotension requiring multiple vasopressors and/or hypoxia requiring CPAP, BPAP, or mechanical ventilation	< 30 kg: Administer tocilizumab ^c 12 mg/kg IV over 1 hour ≥ 30 kg: Administer tocilizumab ^c 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat in 8 hours if no improvement, no more than 3 doses in 24 hours, maximum of 4 doses total.	Dexamethasone 10 mg IV Q6 hours. If refractory consider 3 doses of 1000 mg/day IV of methylprednisolone; If refractory consider dosing every 12 hours followed by rapid taper	ICU care and hemodynamic monitoring; Mechanical ventilation as needed; IV fluid bolus and vasopressors as needed; Symptomatic management of organ toxicities.

Note:

- Perform grading according to ASTCT criteria (2019), and refer to amendments to NCCN guidelines (2022.v1) for the principles of management.
- NCCN Guidelines Version 1, 2022, Management of Immunotherapy-Related Toxicities, CAR T-cell Related Toxicities, Cytokine Release Syndrome
- Refer to tocilizumab Prescribing Information for details.

24.4.2 Immune Effector Cell-associated Neurotoxicity Syndrome (CANS)

(1) Definition and clinical manifestations

Neurological symptoms associated with CAR-T treatment include mental status changes, aphasia, varying degrees of loss of consciousness, and epilepsy or epileptic seizure, which may concurrently occur with CRS or occur alone. CAR T-cell-related encephalopathy syndrome (CRES) can be used to describe neurotoxicity associated with CAR-T cell treatment, and according to 2019 ASTCT consensus, the term IEC-associated neurotoxicity syndrome (ICANS) is put forward, which is defined as “a nervous system disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”

ICANS manifestations are divided into two stages; in the first stage, it concurrently occurs with hyperpyrexia and other CRS symptoms, which is the most common in the first 5 days of cellular immunotherapy; in the second stage, it occurs after the abatement of hyperpyrexia and other CRS symptoms, which is common 5 days after cell infusion. ICANS generally persists for 2-4 days, but the duration varies from hours to weeks. ICANS that occurs concurrently with CRS persists shorter with a lower grade (1-2) compared to ICANS that occurs after CRS, which commonly persists longer with grade > 3.

Refer to the consensus grading of immune effector cell-associated cytokine release syndrome and neurotoxicity issued by ASTCT in 2019 and the guidelines for toxicological assessment and management of cell therapy issued by the University of Texas MD Anderson Cancer Center in 2017 for the severity grading and clinical interventions of neurotoxicity that occurs in this study.

Table 11 ASTCT consensus grading of immune effector cell-associated neurotoxicity syndrome (ICANS) for adults

Neurotoxicity Domain*	Grade 1	Grade 2	Grade 3	Grade 4
ICE score**	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness***	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous/repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical focal seizure or generalized seizure	Life-threatening prolonged seizure (> 5 min) or repetitive

Neurotoxicity Domain*	Grade 1	Grade 2	Grade 3	Grade 4
			that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/Cerebral edema	N/A	N/A	Focal/local cerebral edema on neuroimaging****	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Note:

* Other signs or symptoms that may occur and may be associated with immune effector cell therapy, such as headache, tremor, myoclonus, asterixis, and hallucination, require attention and direct treatment, although not used for ICANS grading.

**One point is given (total score = 10) if any of the following tasks is completed correctly regarding ICE score:

- Orientation: Orientation to year, month, city, hospital (4 points);
- Naming: Name 3 objects, e.g., point to clock, pen, button (3 points);
- Following simple commands, e.g., Show me 2 fingers or close your eyes and stick out your tongue (1 point);
- Write a standard sentence, e.g., "Our national flag is the five-starred red flag" (1 point);
- Count backwards from 100 by ten (1 point).

A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

***Depressed level of consciousness is attributable to no other cause (e.g., no sedating medication).

****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 v 5.0.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause. For example: A patient with an ICE score of 3 may be classified as "grade 3" ICANS if with global aphasia.

(2) Principles for management

Assessment and Supportive Care Recommendations for ICANS (all grades) are presented below:

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for $\geq$ grade 2 neurotoxicity
- Conduct electroencephalogram (EEG) for seizure activity for $\geq$ grade 2 neurotoxicity
- Aspiration precautions; IV hydration
- Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment).

The recommendations on ICANS management are presented in [Table 12](#):

Table 12 Recommendations on management of ICANS

Treatment by Grade	No Concurrent CRS ^x	Additional Therapy if Concurrent CRS
Grade 1 ^v	Supportive care	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose) aa, †
Grade 2	- Supportive care - 1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12hours, if no improvement.	Anti-IL-6 therapy as per Grade 1 ^{aa} Consider transferring patient to ICU if neurotoxicity associated with grade $\geq$ 2 CRS
Grade 3 ^w	- ICU care is recommended - Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours ^{k,y} - Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade $\geq$ 3 neurotoxicity.	Anti-IL-6 therapy as per Grade 1 ^{aa}
Grade 4 ^w	- ICU care, consider mechanical ventilation for airway protection. - High-dose corticosteroids ^{k,z} - Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade $\geq$ 3 neurotoxicity. - Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per Grade 1 ^{aa}

Note:

† Under conditions of limited tocilizumab availability, consider one of the following conservation

strategies:

- Limit tocilizumab use to a maximum of 2 doses during a CRS episode
 - Consider using steroids more aggressively during a CRS episode
 - If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.
- k Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.
- v For lisocabtagene maraleucel or idecabtagene vicleucel, if ICANS develops < 72 hours after infusion, consider dexamethasone 10 mg IV every 12–24 hours x 2 doses and reassess.
- w Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure. If intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3–4 neurotoxicity.
- x If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of grade 4 and prolonged neurologic toxicities.
- y For axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 g daily for 3–5 days may be preferable.
- z For example, methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
- aa Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

Table 13 Management of status epilepticus after cell treatment

Nonconvulsive status epilepticus	1. Assess airway, respiration and blood circulation, and have blood sugar test. 2. Lorazepam 0.5 mg IV and additional 0.5 mg IV every 5 minutes as needed (up to 2 mg) to control fit. 3. Levetiracetam 500 mg IV push, used as the maintenance dose. 4. For status epilepticus, phenobarbital IV at a loading dose of 60 mg. 5. The maintenance dose after nonconvulsive status epilepticus is relieved is as follows: lorazepam 0.5 mg IV q8h, a total of 3 doses; levetiracetam 1000 mg IV q12h; phenobarbital sodium 30 mg IV q12h.
Convulsive status epilepticus	1. Assess airway, respiration and blood circulation, and have blood sugar test. 2. Transfer to the ICU for joint diagnosis and treatment by the investigator and the ICU physician. 3. Lorazepam 2 mg IV and additional 2 mg to a total dose of 4 mg to control epileptic seizures. 4. Levetiracetam 500 mg IV push, used as the maintenance dose. 5. For status epilepticus, phenobarbital IV at a loading dose of 15 mg/kg 6. The maintenance dose after convulsive status epilepticus is relieved is as follows: lorazepam 0.5 mg IV q8h, a total of 3 doses; levetiracetam 1000 mg IV q12h; phenobarbital 1–3 mg/kg IV q12h. 7. If refractory epilepsy, continue EEG monitoring.

Table 14 Management of intracranial pressure increased after cell infusion

Grade 1-2 papilledema with cerebrospinal fluid pressure < 20 mmHg and without cerebral edema	Administer acetazolamide 1000 mg iv, followed by 250-1000 mg iv 1/12h (adjust the dose according to renal function and acid-base balance, monitor once to twice a day).
Grade 3-5 papilledema with imaging examination-indicative cerebral edema, or cerebrospinal fluid pressure ≥ 20 mmHg	1. High-dose glucocorticoid treatment, refer to the recommendations (Table 12) on the management of grade 4 immune effector cell-associated neurotoxicity (ICANS); 2. Raise the head of the bed by 30° for the patient; 3. Maintain hyperventilation to maintain partial arterial pressure of carbon dioxide (PaCO₂) of 28-30 mmHg, but not more than 24 hours; 4. Hypertonic treatment: mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%); (1) Mannitol: initial dose is 0.5-1 g/Kg, maintenance dose is 0.25-1 g/Kg for 1/6h, monitor metabolic parameters and serum osmolality every 6 hours. If serum osmolality is ≥ 320 mOsm/kg or osmotic pressure difference is ≥ 40, stop mannitol; (2) Hypertonic saline: initial dose is 3% hypertonic saline 250 ml; maintenance dose is 50-75 ml/h, monitor electrolytes every 4 hours. If serum sodium ion level reaches ≥ 155 mEq/l, stop the infusion; (3) For patients with imminent brain herniation: initial dose is 23.4% hypertonic saline 30 ml, if necessary, repeat the dose after 15 minutes; 5. If the patient has an ommaya reservoir, drain the cerebrospinal fluid so that the cerebrospinal fluid pressure is < 20 mmHg; 6. When EEG shows burst suppression activity, hold group consultation in neurosurgery department for collaborative diagnosis and treatment; 7. Monitor metabolic parameters every 6 hours, perform head CT every day, and adjust the above medications according to the clinical situation to prevent rebound cerebral edema, renal failure, electrolyte disturbance, hypovolemia and hypotension.

Note:

Papilledema is graded according to the revised Frisén scale³.

References:

- Lee, D. W. et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol. Blood Marrow Transplant.* 25, 625-638 (2019).
- Frisen, L. Swelling of the optic nerve head: a staging scheme. *J. Neurol. Neurosurg. Psychiatry* 45, 13-18 (1982).
- Hill JA, Giralt S, Torgerson TR, Lazarus HM. CAR-T - and a side order of IgG, to go? - Immunoglobulin replacement in patients receiving CAR-T cell therapy. *Blood Rev.* 2019 Nov;38:100596.

24.5 Appendix 5 Line of Treatment

1. Definition of line of treatment:

Treatment with a single drug or a combination of several drugs for ≥ 1 cycle, or planned sequential therapy (initial induction therapy + hematopoietic stem cell transplantation + consolidation therapy + maintenance therapy) is recorded as one line.

Table 15 Definition of the number of prior lines of therapy in multiple myeloma

Definition of a New Line of Treatment	Note
Discontinuation of 1 treatment regimen and start of another*	The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted. It is recognized that reasons for change may include end of planned therapy, toxicity, progression, lack of response, inadequate response, etc.
Unplanned addition or substitution of 1 or more drugs in a regimen	
In patients undergoing > 1 SCT, each SCT (autologous or allogeneic) is considered a new line of therapy	Note that a planned tandem SCT is an exception and is considered 1 line. Planned induction and/or consolidation, maintenance with any SCT (frontline, relapse, autologous or allogeneic) is considered 1 line.

*It should be noted that:

- A regimen is not considered to have been discontinued if some (but not all) drugs in the regimen have been discontinued;
- A discontinued regimen restarted at a later date will be counted as a new line of therapy if there were 1 or more other regimens administered in between.
- Restarting the same regimen (even with dose modifications) without any other intervening regimen is not considered a new line.;
- The original regimen is interrupted, but a single drug or several drugs is/are additionally administered to continue the treatment, each of which is separately recorded as one line;
- The original regimen only has a dose change and is re-administered, it is only recorded as one line.

2. Examples:

- (1) Lenalidomide plus low-dose dexamethasone (RD) as initial therapy, and due to inadequate response, bortezomib is added (RVD): counted as 2 lines.
- (2) Toxicity with RD as pretransplant induction, and therefore treatment is switched to bortezomib, cyclophosphamide, and dexamethasone (VCD): RD is counted as 1 line; VCD (and subsequent planned SCT) is line 2.

- (3) Posttransplant observation without maintenance, and then, due to paraprotein rise 6 months later, lenalidomide is started, which is not planned maintenance; hence, lenalidomide will be considered as a new line.
- (4) RVD and disease progression at some point, and then VCD is used; then, RVD is used again as a salvage strategy: this is counted as 3 lines.
- (5) RD as initial therapy for 2 years, then stopped due to plateau phase (or any other cause), and then restarted 6 months later due to progression: this should be counted as 1 line.

Reference:

Rajkumar, S. Vincent, Paul Richardson, and Jesus F. San Miguel. "Guidelines for determination of the number of prior lines of therapy in multiple myeloma." *Blood, The Journal of the American Society of Hematology* 126.7 (2015): 921-922.

24.6 Appendix 6 Calculation Formula and Unit Conversion

1. Serum creatinine unit conversion

The actual measurement units of serum creatinine at different study sites include $\mu\text{mol/L}$ and mg/dL . The conversion formula between the two units is: $\mu\text{mol/L} \times 0.01131 = \text{mg/dL}$.

2. Glucocorticoid conversion

cortisone 10 mg = betamethasone 0.3 mg = dexamethasone 0.3 mg = fluometholone 0.5 mg = hydrocortisone 8 mg = methylprednisolone 1.6 mg = prednisolone 2 mg = prednisone 2 mg = triamcinolone 1.6 mg

Reference:

2011. Guidelines for the clinical application of glucocorticoids (Ministry of Health)

3. Calculation of ECG QTcF interval

$QTcF = QT / (RR^{0.33})$, RR is normalized heart rate value, which is obtained from 60 divided by the heart rate.

4. Serum calcium corrected for albumin

Corrected serum calcium (mmol/L) = total serum calcium (mmol/L) - $0.025 \times$ concentration of serum albumin (g/L) + 1.0 (mmol/L)

Corrected serum calcium (mg/dl) = total serum calcium (mg/dl) - concentration of serum albumin (g/L) + 4.0 (mg/dl)

Reference:

Chinese Hematology Association, and Chinese Myeloma Committee-Chinese Hematology Association. "The guidelines for the diagnosis and management of multiple myeloma in China (2020 revision)." *Zhonghua nei ke za zhi* 59.5 (2020): 341-346.