Exploratory Study of Anti-BCMA–CD19 CAR-T Cell Therapy in Relapsed or Refractory IgG4-Related Disease

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Title	Exploratory clinical study of anti-BCMA–CD19 CAR-T cell injection for relapsed or refractory IgG4-related disease.
Protocol Num.	2025-07-15
Planned Enrollment	9 subjects
Objectives	**Primary objective** - To explore the efficacy and safety of anti-BCMA–CD19 CAR-T cell injection for the treatment of relapsed or refractory IgG4-related disease. **Secondary objectives** - To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of the anti-BCMA–CD19 CAR-T cell injection. Exploratory objective - To explore changes in the immune microenvironment of peripheral blood, bone marrow and lesions before and after treatment with the anti-BCMA–CD19 CAR-T cell injection.
End points	**Primary end points** - *Safety end points* ♦ Dose-limiting toxicity (DLT): defined as any grade 3 or higher toxicity related to CAR-T cells occurring within 28 days after infusion. The following are excluded:

	1. Grade 3 cytokine release syndrome (CRS) that responds to appropriate medical intervention within 3 days (recovering to grade 2 or lower). 2. Grade 3/4 tumor lysis syndrome (TLS) lasting less than 7 days. 3. Hematologic toxic effects: (i) any grade 3 neutropenia at any time or grade 4 neutropenia lasting less than 14 days; (ii) any grade 3 anemia at any time or grade 4 anemia lasting less than 14 days; (iii) any grade 3 thrombocytopenia at any time or grade 4 thrombocytopenia lasting less than 21 days; (iv) all other cytopenias except the neutropenia, anemia and thrombocytopenia listed above. 4. Non-hematologic toxic effects: (i) fever of any degree, including febrile neutropenia; (ii) grade 3 diarrhea lasting less than 72 hours; (iii) grade 3 nausea or vomiting lasting less than 72 hours; (iv) grade 3 fatigue lasting less than 7 days. 5. Grade 3/4 elevations of aminotransferases, bilirubin, creatine kinase, blood urea nitrogen or creatinine lasting less than 7 days; (vi) asymptomatic elevation of lipase in the absence of any clinical signs or symptoms of pancreatitis; (vii) any asymptomatic grade 3 non-hematologic laboratory abnormality that is rapidly reversible (returning to baseline or grade 2 or lower within 7 days). ♦ Adverse events, serious adverse events, laboratory abnormalities and the grade and frequency of adverse events of special interest (including CRS and immune effector cell–associated neurotoxicity syndrome [ICANS]). - *Efficacy end points* ♦ Primary efficacy end-point measure: Change from baseline in the IgG4-related disease response index (IgG4-RD RI) at W12 and W26.

	♦ Secondary efficacy end-point measures: 1. Change from baseline in lesion size on imaging at W12 and W26. 2. Change from baseline in IgG4 levels at W12 and W26. 3. Change from baseline in IgE, IgG and absolute eosinophil count at W12 and W26. 4. Change from baseline in histopathology of the lesion at W26 or at the time of peripheral blood B-cell recovery. **Secondary end points** - *Amplification and persistence of anti-BCMA–CD19 CAR-T cells in vivo:* ♦ Main PK parameters: peak expansion (C_{max}), time to peak expansion (T_{max}) and blood exposure. ♦ Main PD parameters: changes in cytokines and levels of $CD19^{+}$B cells. **Exploratory end points** - *Changes in the relative abundance and functional status of key immune cell subsets and B-cell subsets (in peripheral blood, bone marrow and lesion tissue) and related cell-communication factors before and after treatment (baseline and W26).*
Study design	This is a prospective exploratory clinical trial in subjects with relapsed or refractory IgG4-related disease to explore the safety and efficacy of anti-BCMA–CD19 CAR-T cell injection. Cyclophosphamide is a commonly used immunosuppressant for autoimmune diseases, and its adverse-event profile (e.g., nausea) is well understood and generally accepted by patients. In cell therapy, cyclophosphamide is routinely used as a lymphodepletion agent and is combined with fludarabine to enhance lymphodepletion and reduce immune rejection. Studies have

	shown that cyclophosphamide combined with fludarabine lymphodepletion is well tolerated and effective in various immune diseases. Therefore, cyclophosphamide in combination with fludarabine will be used in this study for lymphodepletion. The main study consists of a screening period (D−45 to D−21), an autologous CAR-T cell expansion period (D−20 to D−6), lymphodepletion chemotherapy and rest observation (D−5 to D−1), and a cell-infusion and primary end-point assessment period (D0 to w26 after infusion). After the end of the main study, subjects may enter an extension observation period (w27 to W52 after infusion) if they wish. **Screening period (D−45 to D−21)** After signing an informed-consent form, potential subjects undergo screening procedures to determine eligibility according to inclusion and exclusion criteria. **Autologous CAR-T cell expansion period (D−20 to D−6)** After leukapheresis at the First Medical Center of the Chinese PLAGH, peripheral blood mononuclear cells are transported by cold chain to the Cancer Prevention and Treatment Research Institute of Xuzhou Medical University to prepare the anti-BCMA–CD19 CAR-T cell product. The preparation is expected to take 2 weeks. **Lymphodepletion chemotherapy (D-5 to D−3)** The study uses a 3+3 dose-escalation design and plans to enroll 9 subjects. Lymphodepletion chemotherapy begins 5 days before infusion. The regimen is as follows: (i) Cyclophosphamide: 250 mg/m^2/d, i.v. × 3 days, (D−5 to D−3). (ii) Fludarabine: 30 mg/m^2/d, i.v. × 3 days, (D−5 to D−3).

	For older patients, patients with low blood counts or poor performance status, or patients with abnormal renal function, the dose may be adjusted to reduce the fludarabine dose by 20-50 percent of the standard regimen; cyclophosphamide remains at 250 mg/m^2/d for 3 consecutive days (D−5 to D−3). Investigators may adjust the dose and schedule at his or her discretion according to individual tolerance. Safety, pharmacokinetics and efficacy will be assessed. **Rest observation (D-2 to D−1)** Examinations and assessments will be conducted according to the study protocol. **Cell infusion and primary end-point assessment (D0 to W26 after infusion)** Anti-BCMA–CD19 CAR-T cells will be infused intravenously 2 days after completion of lymphodepletion chemotherapy (D0). Efficacy and safety evaluations will be performed before infusion, during infusion and at multiple time points afterward (on the infusion day and on D3, D7, D10 and W2, 3, 4, 8, 12, 16, 20 and 26 after infusion). Efficacy evaluations will be conducted at W2, 4, 8, 12, 16, 20 and 26 after infusion. Additional assessments may be performed at the investigator's discretion. Safety evaluations will include follow-up through W26 after infusion. **Extension observation period (W27 to W52 after infusion)** During this period, efficacy and safety are evaluated. Efficacy assessments will be conducted at W38 and W52 after infusion. Additional assessments may be performed at the investigator's

	discretion. Subjects will be followed for safety through W26 after infusion.
Dose escalation	Previous clinical studies of anti-BCMA–CD19 CAR-T cell injection (ChiCTR2200061267 and ChiCTR2000033567) showed controllable low-grade CRS and no other serious adverse events. This study will continue to use the 3+3 dose-escalation method. Three dose cohorts will be evaluated, each with 3 subjects and allowing a 20% variation in total infused cells: 1. Low-dose cohort: 1×10^6 CAR-T cells/kg. 2. Intermediate-dose cohort: 2×10^6 CAR-T cells/kg. 3. High-dose cohort: 3×10^6 CAR-T cells/kg.
Lymphodepletion chemotherapy	Subjects must be assessed by the investigator as suitable for lymphodepletion; there must be no uncontrolled active infection before chemotherapy, and body temperature must not exceed 38°C within 48 hours before dosing. During D-5 to D-3 before infusion, subjects will receive the prescribed chemotherapy regimen. Investigators may adjust the dose and schedule according to individual tolerance.
Study population and planned number of subjects	Nine patients with relapsed or refractory IgG4-related disease will be recruited.
Inclusion criteria	To participate, subjects must meet all of the following criteria: 1. Aged 18 to 75 years, inclusive, regardless of sex. 2. Meet the 2019 ACR/EULAR classification criteria for IgG4-related disease. 3. Involvement of two or more systems and/or involvement of important organs (including but not limited to the pancreas, bile ducts, kidneys and dura mater). 4. Relapsed or refractory IgG4-related disease: remaining in an active disease state after at least 3 months of glucocorticoid plus rituximab therapy or recurrence of disease activity after

	remission; inability to taper glucocorticoids or relative contraindications to glucocorticoid use (including diabetes, hypertension, osteoporosis, etc.). 5. Important organ function meeting the following conditions: ♦ Bone marrow: (i) neutrophil count ≥1×10^9/L (excluding disease-related neutropenia); (ii) hemoglobin ≥60 g/L. ♦ Hepatic function: ALT≤3×ULN (elevation caused by disease may be excluded); AST≤3×ULN (elevation caused by disease may be excluded); TBIL≤1.5×ULN (elevation caused by disease may be excluded). ♦ Renal function: creatinine clearance (Cockcroft–Gault formula) ≥30 ml/min (excluding acute decline due to disease). ♦ Coagulation: international normalized ratio (INR) ≤ 1.5×ULN, prothrombin time (PT) ≤ 1.5×ULN ♦ Cardiac function: stable hemodynamics. 6. Women of childbearing potential and male subjects with partners of childbearing potential must use medically accepted contraception or abstain during study treatment and for at least 12 months after the end of treatment. Women of childbearing potential must have a negative serum HCG test within 7 days before enrollment and must not be breastfeeding. 7. Voluntary participation in this clinical study with signed informed consent and willingness to comply with study procedures and follow-up. 8. Patent superficial peripheral veins adequate for intravenous infusion.
Exclusion criteria	Subjects will be excluded if any of the following criteria are met: 1. History of severe drug allergy or allergic constitution. 2. Current or suspected uncontrollable or treatment-requiring fungal, bacterial, viral or other infections.

	3. Central nervous system disease (excluding disease-related epilepsy, psychosis, organic brain syndrome, cerebrovascular accident, encephalitis or central nervous system vasculitis). 4. Cardiac insufficiency that precludes participation. 5. Congenital immunoglobulin deficiency. 6. Congenital malformation or nutritional disorder causing severe organ impairment. 7. History of malignancy within the past five years. 8. End-stage renal failure. 9. Positive hepatitis B surface antigen and hepatitis B core antibody with HBV-DNA titers above the assay limit of detection; positive hepatitis C antibody with HCV-RNA positivity; positive human immunodeficiency virus antibody; positive syphilis serology. 10. Psychiatric disorders or severe cognitive impairment. 11. Participation in other clinical trials within three months before enrollment. 12. Receipt of any investigational drug within 12 weeks before screening or within five half-lives of the agent (whichever is longer). 13. Pregnant or intending to become pregnant. 14. Any other reason deemed by the investigator to preclude enrollment.
Investigational drug, dose and administration	Three dose cohorts of anti-BCMA–CD19 CAR-T cell injection (1×10^6, 2×10^6 and 3×10^6 CAR-T cells/kg) will be evaluated sequentially, with the total number of cells allowed to vary by ± 20%. The product is administered intravenously. The investigator may adjust the dose according to clinical judgment.
Statistical methods	After completion of the study and locking of the database, data will be analyzed by the collaborator or a designated contract research organization. Statistical programming and analyses will be performed using SAS and/or other validated statistical software.

IPD Sharing Plan	De-identified individual participant data (IPD) — including baseline characteristics, outcome measures, adverse events, and laboratory results — will be shared, along with the final study protocol, informed consent form, and statistical analysis plan. Access will be granted to qualified researchers from academic or medical institutions upon submission of a scientifically sound and ethically appropriate proposal. Requests will be reviewed by the sponsor and principal investigator. Approved researchers must sign a data use agreement (DUA). Data will be available after publication of the main results or within 6 months after study completion (whichever is earlier), first hosted on the principal investigator's GitHub repository and later transferred to a secure institutional platform.