Protocol Synopsis

Protocol Number: CT-P10 3.4
Title: A Phase 3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Compare Efficacy and Safety between CT-P10 and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma
Sponsor: CELLTRION, Inc., 23, Academy-ro, Yeonsu-gu, Incheon, 22014, South Korea
Study Phase: Phase 3
Study Centres: It is expected that up to approximately 125 study centres in Europe, Africa, the Middle East, Asia Pacific, and Latin and North America will be included in this study.
Indication: Follicular lymphoma
Rationale: CT-P10 is being developed as a proposed biosimilar product of Rituxan (rituximab). Rituximab is a suggested treatment regimen as a single-agent first-line therapy for patients with follicular lymphoma (FL). This study includes a rituximab maintenance therapy regimen in patients with Grade 1 to 3a (Ann Arbor stage II-IV) low tumour burden follicular lymphoma (LTBFL) based on Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria. The proposed dosing regimen is in line with the approved labelling for Rituxan. Rituximab maintenance therapy (as both Rituxan and MabThera) has demonstrated improved progression-free survival in patients with FL in Phase 3 clinical studies. The overall safety profile of CT-P10 is expected to mirror that of Rituxan. The most common adverse reactions of Rituxan (incidence 25%) observed in clinical trials of patients with non-Hodgkin's lymphoma (NHL) were infusion reactions, fever, lymphopenia, chills, infection, and asthenia. The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P10 administration. This study is designed to demonstrate similarity in efficacy and safety of CT-P10 compared with Rituxan in patients with low tumour burden FL.
Test Formulation, Dose, and Regimen: CT-P10 (375 mg/m^2 intravenous [IV])
Reference Drug, Dose, and Regimen: US-licensed Rituxan (375 mg/m^2 IV)
Route of Administration: CT-P10 or Rituxan 375 mg/m^2 diluted in normal saline will be administered as an IV infusion weekly for 4 weeks during the Induction Study Period. CT-P10 or Rituxan (375 mg/m^2 IV) will be administered as maintenance in patients who have a disease control (complete response [CR], unconfirmed complete response [CRu], partial response [PR] or stable disease [SD]) after the completion of the Induction Study Period. The Maintenance Study Period will be continued up to maximum 12 cycles for 2 years, with study drug (either CT-P10 or Rituxan) administered every 8 weeks for a maximum of 6 cycles for 1 year. After the 1st year of Maintenance Period (MP1), once the similarity between study drugs is confirmed, additional CT-P10 administration will be offered to all patients who have completed MP1 at discretion of participating investigator. The total infusion of the maintenance treatment will not exceed 12 cycles over 2 years.
Objectives: Primary Objective: To demonstrate that CT-P10 is similar to Rituxan in terms of efficacy as determined by overall response rate (CR + CRu + PR) at 7 months (Prior to Cycle 3 of the Maintenance Study Period) according to the Modified Response Criteria for Malignant Lymphoma.

Secondary Objectives:

- To evaluate overall response rate (CR + CRu + PR) according to the Modified Response Criteria for Malignant Lymphoma during the study period.
- To evaluate additional efficacy parameters (progression-free survival, time to progression and overall survival according to the Modified Response Criteria for Malignant Lymphoma).
- To evaluate pharmacokinetics**,** pharmacodynamics (B-lymphocyte [B-cell] kinetics), overall safety including immunogenicity, and biomarkers of CT-P10 in comparison with Rituxan.

Patient Population: Male or female patients 18 years or older, with a histologically confirmed FL of grade 1 to 3a (according to the World Health Organization 2008 classification); Ann Arbor stage II, III or IV disease; low tumour burden; at least 1 measurable tumour mass; confirmed CD20+ lymphoma; Eastern Cooperative Oncology Group performance status of 0 to 1; and adequate bone marrow, hepatic, and renal function reserve.

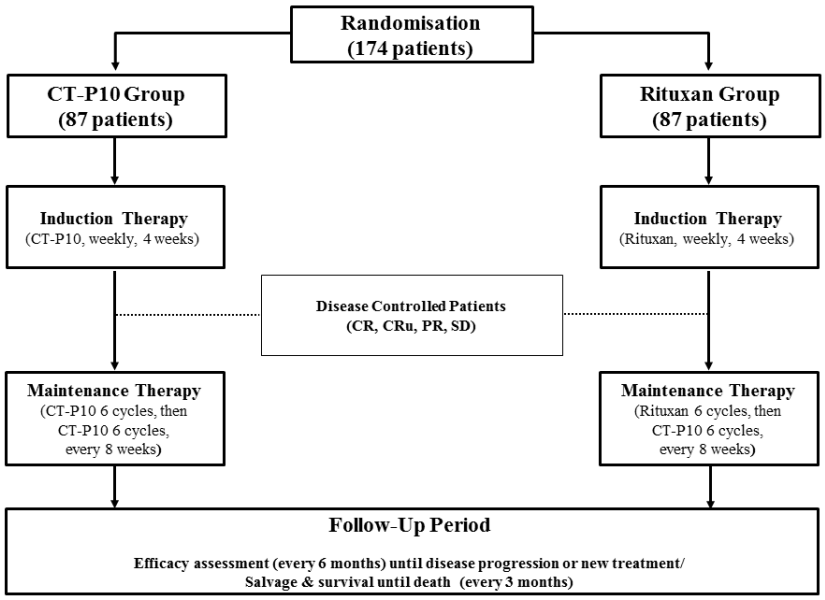
Study Design: This is a Phase 3 prospective, randomised, parallel-group, active-controlled, double-blind, multicentre, international study designed to evaluate the similarity in efficacy (overall response rate [ORR]), of CT-P10 compared with Rituxan and safety in patients with stage II-IV low tumour burden FL.

There will be 4 periods in the study:

- Screening Period (up to 6 weeks)
- Induction Study Period (up to 4 weeks)
- Maintenance Study Period (up to maximum 12 cycles for 2 years) in patients with CR, CRu, PR or SD after the completion of the Induction Study Period
- Follow-up Period (up to 27 months from Day 1 of Cycle 1 of the Induction Study Period for the last enrolled patient)

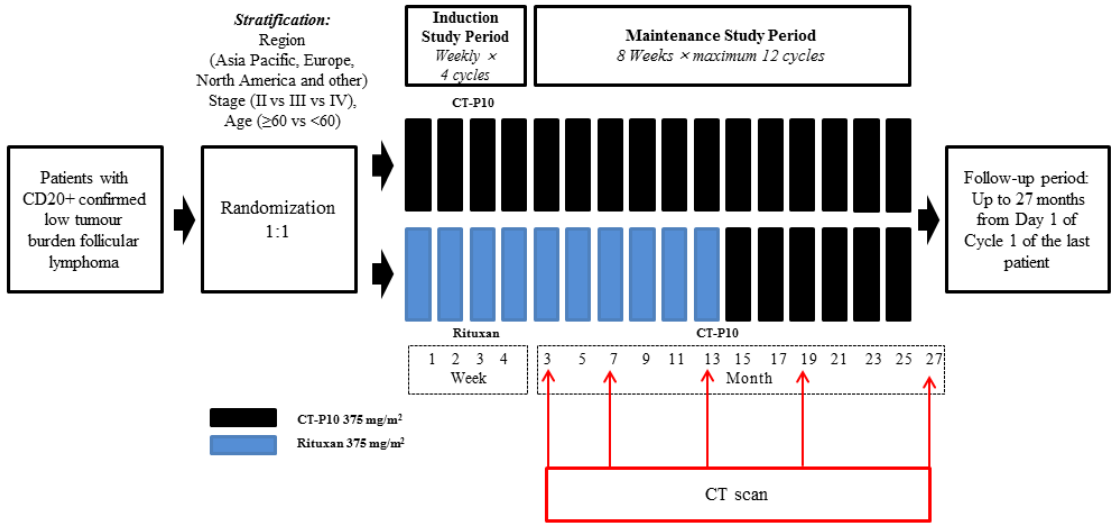
A schematic of the study design is presented in Figure S1 and dose schedule in Figure S2.

Figure S1 Study Design



Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease

Figure S2 Dose Schedule



Abbreviations: CT, computed tomography

Efficacy Assessments: Efficacy will be assessed using computed tomography (CT) with contrast with or without magnetic resonance imaging, bone marrow examination, B-symptoms, physical examination on tumour site and lactate dehydrogenase level.

Primary Efficacy Endpoint:

The primary efficacy endpoint is:

- Overall response rate (CR + CRu + PR) at 7 months (Prior to Cycle 3 of the Maintenance Study Period), according to the Modified Response Criteria for Malignant Lymphoma

Secondary Efficacy Endpoints:

The following efficacy parameters for the study drug will be determined as secondary endpoints:

- Overall response rate (CR + CRu + PR) during the study period
- Progression-free survival, defined as the interval between randomisation and disease progression/relapse, or death from any cause, whichever occurs first
- Time to progression, defined as the interval between randomisation and disease progression/relapse or death as a result of lymphoma, whichever occurs first
- Overall survival, defined as the interval between randomisation and death from any cause

Pharmacokinetic Assessments: Blood samples for pharmacokinetic (PK) analysis will be obtained at;

- Day 1 of Cycle 1-4 of the Induction Study Period and Day 1 of Cycles 1-2 of the Maintenance Study Period: predose and 1 hour after the end of infusion
- Day 1 of Cycle 3 of Maintenance Study Period: predose
- First EOT and Second EOT visit: any time of the day

Secondary PK Endpoints:

- Maximum serum concentration (C_{max}) at each dose
- Trough serum concentration (C_{trough}) at each dose

Pharmacodynamic Assessments: Blood samples for pharmacodynamic (PD) analysis will be obtained at;

- Day 1 of Cycle 1 of the Induction Study Period and Day 1 of Cycles 1-2 of the Maintenance Study Period: predose and 1 hour after the end of infusion
- Day 1 of Cycle 2-4 of the Induction Study Period and Day 1 of Cycle 3 of Maintenance Study Period: predose
- First EOT and Second EOT visit: any time of the day

Secondary PD Endpoint:

- B-cell kinetics

Safety Assessments:

- Adverse events, serious adverse events, concomitant medications, hypersensitivity (via vital signs monitoring including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), physical examination findings, vital sign measurements, clinical laboratory analyses, chest x-ray findings, electrocardiogram findings, infection, infusion-related reactions, immunogenicity testing, immunoglobulin testing, and tuberculosis assessment.

Biomarker Assessment (Optional): Only for patients who sign a separate informed consent form (ICF) for the biomarker assessment (genotypes). A blood sample for evaluation of FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected after randomisation and before study drug administration on Day 1 of Cycle 1 during the Induction Study Period only.

Secondary Biomarker Endpoint:

- FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes)

Sample Size:
A sample size of 174 patients (87 patients in each treatment group of CT-P10 and Rituxan) leads to 91% statistical power for the demonstration of similarity of ORR at 7 months (Prior to Cycle 3 of the Maintenance Study Period) based on ORR of 88% and an equivalence margin of ±17% using a 2-sided 90% confidence intervals (CIs) approach corresponding to 5% significance level of an equivalence test. The intent-to-treat (ITT) population will be the primary analysis population for the efficacy analysis. A supportive analysis for the efficacy analysis will be conducted using the per-protocol (PP) population for response rate. In the PP population with a 13% drop-out rate, 86% statistical power is expected.

Inclusion Criteria:
Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female ≥18 years.
2. Patient has histologically confirmed CD20+ FL grade 1 to 3a according to the World Health Organization 2008 classification; biopsy within 6 months before the first administration of the study drug.
3. Patient has at least 1 measurable tumour mass in 2 dimensions, and the mass must be:
   - Nodal lesion >15 mm in the longest dimension; or
   - Nodal lesion >10 mm to ≤15 mm in the longest dimension and >10 mm in the shortest dimension; or
   - Extranodal lesion with both long and short dimensions ≥10 mm.
4. Patient has Ann Arbor stage II, III, or IV disease.

5. Patient has low tumour burden, defined as based on Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria:
   - No B symptoms,
   - LDH < upper limit of normal (ULN),
   - Largest nodal or extra mass <7 cm,
   - <3 nodal sites with a diameter ≥3 cm,
   - No significant serous effusions detectable clinically or on CT (small, clinically non-evident effusions on CT scan are not deemed significant),
   - Spleen ≤16 cm by CT, and
   - No clinical organ failure or organ compression (e.g. ureteric obstruction)
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
7. For both male and female patients and their partners of childbearing potential, patient agrees to practice true abstinence (when this is in line with preferred and usual lifestyle of the subject) or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilised):
   - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
   - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
   - Intrauterine devices

   Male or female patients and their partners who have been surgically sterilised for less than 6 months prior to the first administration of the study drug must agree to use 1 medically acceptable method of contraception or practice true abstinence during study treatment.
   Menopausal females must have experienced their last period more than 12 months prior to study entry (ie, when the informed consent form [ICF] is signed) to be classified as not of childbearing potential.
   For both premenopausal women and women who are less than or equal to 12 months after the onset of menopause, patient has a negative serum pregnancy test during the Screening Period.
8. Patient has adequate bone marrow, hepatic, and renal function reserve as evidenced by:
   - Haemoglobin level of ≥10 g/dL
   - Absolute neutrophil count of ≥1500/mm^3
   - Platelet count of ≥100 000/mm^3
   - Total bilirubin level of ≤2.0 mg/dL
   - Aspartate aminotransferase and alanine aminotransferase levels of ≤3 times the ULN for the reference laboratory (≤5 × ULN for the reference laboratory with known hepatic involvement by lymphoma)
   - A serum creatinine level of ≤1.5 × ULN for the reference laboratory, or a calculated creatinine clearance by the Cockcroft-Gault equation of ≥50 mL/min
9. Patient is able to understand verbal and/or written instructions and comply with all study requirements.
10. Patient is informed, given ample time and opportunity to read and/or understand about participation in the study, and has signed and dated the written ICF.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Patient has received rituximab (or a rituximab proposed biosimilar product).
2. Patient has allergies or hypersensitivity to contrast agents for radiograph, murine, chimeric, human or humanised proteins.
3. Patient has evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.
4. Patient has known central nervous system involvement or any evidence of spinal cord compression by lymphoma.
5. Patient has received previous treatment for NHL:
   - Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy).
   - All doses of corticoid therapy for treatment of NHL.
   - Corticoid therapy within 4 weeks before the first administration of the study drug, with prednisone >20 mg per day (or equivalent doses of other steroid medications) for any purpose except NHL.
6. Patient has a severe infection, such as sepsis, abscesses, active tuberculosis (TB), or opportunistic infections.
7. Patient has a known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (carriers of hepatitis B and hepatitis C are not permitted to enrol into the study).
8. Patient has New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the previous 6 months before the first administration of the study drug.
9. Patient has any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within the 5 years before the first administration of the study drug.
10. Patient has a current or recent treatment (within 42 days before the first administration of the study drug or 5 times the half-life, whichever is longer, prior to screening) with any other investigational medicinal product or device.
11. Patient has uncontrolled diabetes mellitus, even after insulin treatment.
12. Patient is pregnant or lactating. Patients who are planning to be pregnant or to breastfeed before, during, or within 12 months after the last administration of the study drug are not permitted to enrol into the study.
13. Patient is taking a live, live-attenuated, or nonlive vaccine within 4 weeks before the first administration of the study drug.
14. Patient has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, unstable pulmonary condition, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, or patient is high risk for treatment complications at the investigator’s discretion.

Statistical Methods:
Statistical analysis will be performed using SAS software Version 9.1.3 or later (SAS Institute, Inc, Cary, North Carolina). The data documented in this study and the clinical parameters measured will be described using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for quantitative variables and frequency counts and percentages for qualitative variables. Data will be listed in data listings.

Assigning Patients to Treatment Groups: Patients will be randomly assigned to treatment groups using a computer-generated randomisation schedule prepared before the study. The randomisation will be balanced by using permuted blocks and will be stratified by region (Asia Pacific, Europe, North America and other), stage (II vs III vs IV) and age (≥60 vs <60 years).

Efficacy Analyses:

Primary: The primary efficacy endpoint is the overall response rate (CR + CRu + PR) at 7 months (Prior to Cycle 3 of the Maintenance Study Period), according to the Modified Response Criteria for Malignant Lymphoma. The proportion of overall responders (CR + CRu + PR) at 7 months will be compared between CT-P10 and Rituxan using an exact binomial method, calculating a point estimate and 90% CIs for the difference in proportion between the 2 treatment groups. The 2-sided 90% CIs for the true difference between CT-P10 and Rituxan should be entirely within the equivalence margin of ±17%, then similarity of CT-P10 to Rituxan with respect to response rates will be claimed for this endpoint. The primary population for this analysis will be the ITT population (defined as all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was completed). Overall response rate in the PP population (defined as all randomly assigned patients who have at least 1 response evaluation after receiving at least 1 treatment cycle in the Induction Study Period and who do not have any major protocol violation that may affect the interpretation of study results of efficacy.) will also be tested as supportive result.

Secondary: The first secondary efficacy endpoint is the overall response rate (CR + CRu + PR) during the study period according to the Modified Response Criteria for Malignant Lymphoma; this will be listed and summarised for the ITT population and the PP population.

A sensitivity analysis will be performed on the primary efficacy endpoint, utilising a logistic regression model with covariates. The resulting odds ratio and 90% CIs will be converted into difference of proportions using the Delta method for the purpose of comparison of proportions in the ITT population and the PP population.

A time-to-event analysis will be undertaken for each of the progression-free survival, time to progression and overall survival in the ITT population; the median time and 95% CIs around the median for each treatment group for each secondary endpoint will be estimated using the Kaplan-Meier method if median time is available otherwise the Kaplan-Meier curves will be presented.

Pharmacokinetic Analyses: The PK endpoints will be calculated using noncompartmental methods (WinNonlin Version 5.1.1 or higher). All PK parameters will be summarised by treatment group. In the standard summary statistics, the geometric mean and coefficient of variation will also be presented. The primary population for this analysis will be the PK population (defined as all patients who receive at least 1 dose [full] of study drug and who have at least 1 posttreatment PK result).

Pharmacodynamic Analyses: B-cell kinetics will be summarised by treatment group. The primary population for this analysis will be the PD population (defined as all patients who receive at least 1 dose [full] of study drug and who have at least 1 posttreatment PD result).

Safety Analyses: The safety evaluations will be performed during the study to measure the safety of CT-P10 and Rituxan. Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities. Adverse events will be graded for severity and the terminology of adverse events will be described according to the Common Terminology Criteria for Adverse Events version 4.03. All safety data will be listed and summarised by treatment group as appropriate. The primary population for this analysis will be the safety population (defined as all randomly assigned patients who receive at least 1 dose [full or partial] of study drug).

Biomarker Analyses: Analyses will be performed on Fcγ receptor genotype by treatment groups. The ITT and PP populations will be used for the analyses.