Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial

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Summary

Background Studies in patients with rheumatoid arthritis have shown that the rituximab biosimilar CT-P10 (Celltrion, Incheon, South Korea) has equivalent efficacy and pharmacokinetics to rituximab. In this phase 3 study, we aimed to assess the non-inferior efficacy and pharmacokinetic equivalence of CT-P10 compared with rituximab, when used in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with newly diagnosed advanced-stage follicular lymphoma.

Methods In this ongoing, randomised, double-blind, parallel-group, active-controlled study, patients aged 18 years or older with Ann Arbor stage III–IV follicular lymphoma were assigned 1:1 to CVP plus intravenous infusions of 375 mg/m² CT-P10 or rituximab on day 1 of eight 21-day cycles. Randomisation was done by the investigators using an interactive web or voice response system and a computer-generated randomisation schedule, prepared by a clinical research organisation. Randomisation was balanced using permuted blocks and was stratified by country, gender, and Follicular Lymphoma International Prognostic Index score (0–2 *vs* 3–5). Study teams from the sponsor and clinical research organisation, investigators, and patients were masked to treatment assignment. The study was divided into two parts: part 1 assessing equivalence of pharmacokinetics (in the pharmacokinetics subset), and part 2 assessing efficacy in all randomised patients (patients from the pharmacokinetics subset plus additional patients enrolled in part 2). Equivalence of pharmacokinetics was shown if the 90% CIs for the geometric mean ratio of CT-P10 to rituximab in AUCτ and C_{maxSS} were within the bounds of the equivalence margin of 80% and 125%. Non-inferiority of response was shown if the one-sided 97·5% CI lay on the positive side of the –7% margin, using a one-sided test done at the 2·5% significance level. The primary efficacy endpoint was the proportion of patients who had an overall response over eight cycles and was assessed in the efficacy population (all randomised patients). The primary pharmacokinetic endpoints were area under the serum concentration–time curve at steady state (AUCτ) and maximum serum concentration at steady state (C_{maxSS}) at cycle 4, assessed in the pharmokinetic population. This trial is registered with ClinicalTrials.gov, number NCT02162771.

Findings Between July 28, 2014, and Dec 29, 2015, 140 patients were enrolled. Here we report data for the eight-cycle induction period, up to week 24. The proportion of patients with an overall response in the efficacy population was 64 (97·0%) of 66 patients in the CT-P10 treatment group and 63 (92·6%) of 68 patients in the rituximab treatment group (4·3%; one-sided 97·5% CI –4·25), which lay on the positive side of the predefined non-inferiority margin. The ratio of geometric least squares means (CT-P10/rituximab) was 102·25% (90% CI 94·05–111·17) for AUCτ and 100·67% (93·84–108·00) for C_{maxSS}, with all CIs within the bioequivalence margin of 80–125%. Treatment-emergent adverse events were reported for 58 (83%) of 70 patients in the CT-P10 treatment group and 56 (80%) of 70 in the rituximab treatment group. The most common grade 3 or 4 treatment-emergent adverse event in each treatment group was neutropenia (grade 3, 15 [21%] of 70 patients in the CT-P10 group and seven [10%] of 70 patients in the rituximab group). The proportion of patients who experienced at least one treatment-emergent serious adverse event was 16 (23%) of 70 patients in the CT-P10 group and nine (13%) of 70 patients in the rituximab group.

Interpretation In this study, we show that CT-P10 exhibits non-inferior efficacy and pharmacokinetic equivalence to rituximab. The safety profile of CT-P10 was comparable to that of rituximab. CT-P10 might represent a new therapeutic option for advanced-stage follicular lymphoma.

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Research in context

Evidence before this study

We searched PubMed using the terms "rituximab" AND "biosimilar" or "rituximab" AND "CT-P10" for articles published between Jan 1, 2010, and Aug 6, 2016, not restricted to the English language. We found 46 articles, of which six were clinical studies. Preliminary data indicate that various biosimilars for rituximab are in development and that the clinical equivalence or comparability of these products with rituximab is under extensive investigation. However, published results from randomised clinical trials are minimal. Rituximab biosimilars have the potential to increase accessibility to treatment by lowering treatment costs. Extrapolation of approval to all indications for which the reference product is approved is also permitted, as long as this is scientifically justifiable. Therefore, randomised clinical trials for rituximab biosimilars are pertinent and could change the treatment landscape for a range of B-cell malignancies and B-cell-mediated immune-associated diseases.

Added value of this study

To our knowledge, this is one of the first phase 3 clinical trials of a rituximab biosimilar in patients with a B-cell-related haematological malignancy to be published in full. We found that the rituximab biosimilar CT-P10 has non-inferior efficacy, equivalent pharmacokinetics, and similar pharmacodynamics to rituximab in patients with stage III–IV follicular lymphoma. Furthermore, CT-P10 was well tolerated and the safety and immunogenicity profiles of CT-P10 were similar to that of rituximab.

Implications of all the available evidence

This randomised controlled phase 3 study supports previous preclinical and clinical data showing the biosimilarity of CT-P10 to rituximab. Other clinical trials have shown the equivalence in efficacy and pharmacokinetics of CT-P10 and rituximab in patients with rheumatoid arthritis and here we show that efficacy non-inferiority and pharmacokinetic equivalence can also be shown for patients with advanced-stage follicular lymphoma, supporting extrapolation of biosimilarity across indications. CT-P10 represents the first rituximab biosimilar approved by the European Medicines Agency. Because biosimilars are generally more affordable than innovator products, the availability of CT-P10 might increase access to this important therapeutic option.

Introduction

Rituximab is an anti-CD20 monoclonal antibody widely used in the treatment of B-cell non-Hodgkin lymphoma, including follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic lymphoma, as well as in immune-related diseases such as rheumatoid arthritis. In follicular lymphoma, rituximab (MabThera, Roche Pharma AG, Grenzach-Wyhlen, Germany; Rituxan, Genentech, Inc, California, USA) is approved for use in patients with advanced (stage III–IV) disease, based on the results of several clinical trials[1–5] showing it significantly improved clinical responses and overall survival. Initial approval of rituximab in newly diagnosed advanced follicular lymphoma was as part of the rituximab plus cyclophosphamide, vincristine, and prednisone (CVP) regimen. Although the pivotal role of rituximab in the treatment of advanced-stage follicular lymphoma is recognised in key treatment guidelines,[6,7] its higher costs compared with conventional treatment can restrict access to rituximab in some populations.

CT-P10 is a biosimilar of rituximab approved by the European Medicines Agency (EMA) and the Korean Ministry of Food and Drug Safety in all indications for which rituximab is approved, namely non-Hodgkin lymphoma (including follicular lymphoma and CD20-positive diffuse large B-cell lymphoma), chronic lymphocytic lymphoma, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. CT-P10 shares with its reference product an identical primary structure and highly similar higher-order structures, aggregate or monomeric purities, and post-translational modifications. A phase 1 randomised controlled trial (RCT)[8] in patients with rheumatoid arthritis showed that CT-P10 and European-sourced rituximab (MabThera) have equivalent pharmacokinetics and comparable efficacy, pharmacodynamics, immunogenicity, and safety. In a subsequent phase 3 RCT in patients with rheumatoid arthritis,[9,10] the efficacy and pharmacokinetics of CT-P10 were equivalent to both approved versions of rituximab (MabThera and US-sourced rituximab, Rituxan).

According to the US Food and Drug Administration (FDA), a biosimilar can be defined as a product that is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that shows "no clinically meaningful differences [to] the reference product in terms of safety, purity, and potency".[11] Biosimilars are usually available at a lower price than their reference products and can therefore increase access to biologic therapy. Indeed, a budget impact analysis[12] of CT-P10 predicts that the introduction of CT-P10 in Europe will be associated with significant budget savings and might increase patient access to rituximab treatment. Before approving a biosimilar, regulatory authorities usually require proven equivalence in clinical efficacy and pharmacokinetics between the biosimilar candidate and its innovator biologic or reference product, plus evidence of similar clinical safety and immunogenicity.[11,13]

In this multinational phase 3 RCT, we aimed to assess the non-inferior efficacy and pharmacokinetic equivalence of CT-P10 to rituximab, when used in combination with CVP in patients with newly diagnosed advanced-stage follicular lymphoma. We also compared the pharmacodynamics, safety, and immunogenicity of CT-P10 and rituximab.

Methods

Study design and patients

This ongoing randomised, double-blind, parallel-group, active-controlled, phase 3 study (NCT02162771) was done in 65 centres (including one good clinical practice non-compliant study centre—these patients were excluded from inclusion in all study populations and analyses) in Europe, Africa, Asia Pacific, and Latin America (appendix pp 3, 4). Patients aged 18 years or older with histologically confirmed follicular lymphoma according to WHO 2008 classification[14] were eligible for the study if they had at least one measurable tumour mass that had not previously been irradiated; confirmed CD20-positive lymphoma of grade 1–3a based on local laboratory review; Ann Arbor stage III or IV disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate bone marrow, hepatic, and renal function. Individuals were excluded if they had previously received treatment for non-Hodgkin lymphoma; if they had previously received rituximab (or a rituximab biosimilar), cyclophosphamide, or vincristine (or had experienced allergies or hypersensitivity to these drugs, prednisone, or murine, chimeric, human, or humanised proteins); or had evidence of histological transformation to high-grade or diffuse large B-cell lymphoma. Full eligibility criteria are in the appendix (pp 1, 2).

The protocol was approved by each centre's ethics committee and the relevant regulatory authorities. The study was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

The study was divided into two parts to show equivalence of pharmacokinetics in the pharmacokinetic subset (part 1) and non-inferiority of efficacy in the efficacy population (all randomised patients with at least one response evaluation after receiving at least one full treatment cycle in the induction period and who had no major protocol deviation to the efficacy endpoint; part 2) for CT-P10 compared with rituximab. Patients from the pharmacokinetic subset plus additional patients were enrolled in part 2 to form the all randomised patient population. Patients were randomly assigned 1:1 to receive either intravenous infusions of CT-P10 or US-sourced rituximab. Randomisation was done by the investigators using an interactive web or voice response system and a computer-generated randomisation schedule, prepared by a clinical research organisation. Randomisation was balanced using permuted blocks and was stratified by country, gender, and Follicular Lymphoma International Prognostic Index (FLIPI) score (0–2 *vs* 3–5). Study teams from the sponsor and clinical research organisation, investigators, and patients were masked to treatment assignment (appendix p 5). Briefly, CT-P10 and rituximab were supplied in identical kits that were identified by a unique material number. Material numbers were assigned by interactive web or voice response system based on the randomly assigned treatment group. To allow reporting of available data, the study was partially unmasked at two protocol-defined timepoints after patients in the pharmacokinetic population subset completed cycle 4 (April 4, 2016) and after patients in the all randomised patient population completed the induction period (Sept 30, 2016), for two predefined teams from the sponsor and clinical research organisation. The study will remain masked to the other relevant study teams from the sponsor and clinical research organisation, investigators, and patients until all patients have completed the study and the database has been finalised for study termination.

See Online for appendix

Procedures

Patients received intravenous infusions of 375 mg/m² CT-P10 (Celltrion, Incheon, South Korea) or US-sourced rituximab (Rituxan, Genentech, CA, USA) on day 1 of each 21-day cycle for eight cycles (induction period). All patients were also administered cyclophosphamide (750 mg/m² intravenous infusion on day 1 of each 21-day cycle), vincristine (1·4 mg/m² intravenous infusion [maximum 2 mg] on day 1 of each 21-day cycle), and prednisone or prednisolone (40 mg/m² orally on days 1–5 of each 21-day cycle). Paracetamol (500 mg, oral) and H1 antihistamine (oral or intravenous) were administered before study drug infusion. Response to treatment was assessed after cycles 4 (week 12) and 8 (week 24) during the induction period. Dose reductions were not permitted for CT-P10 or for rituximab. For CVP, prednisone dose modifications were not permitted during the induction period (ie, up to week 24), cyclophosphamide dose could be reduced a maximum of two times, and vincristine could only be reduced once. Discontinuation of cyclophosphamide, or vincristine, or both was also permitted during this period.

Patients with complete response, unconfirmed complete response, or partial response after week 24 of the induction period (as assessed at the first end-of-treatment visit) continued to receive treatment with intravenous CT-P10 or rituximab at 375 mg/m² once every 2 months (up to 2 years; maintenance period). Patients with no response or disease progression after 24 weeks were discontinued from the study. The study is ongoing for assessment of disease progression and overall survival (follow-up is planned until death or 3 years from the first day of cycle 1 of the induction period for the last patient). Here we report findings from the eight-cycle induction period of the study, up to week 24.

Efficacy measurements included CT assessment of tumours using contrast (with or without MRI and PET or PET-CT). The baseline measurement was obtained within 4 weeks before the first day of cycle 1. Additional measurements were taken after week 12 and at the end-of-treatment visit for the induction period. Assessment

of B-symptoms and serum lactate dehydrogenase level were done at the same time as the tumour assessments. A physical examination was done at every visit. Bone marrow biopsies were taken during the screening period (except for patients with a history of bone marrow involvement). An additional biopsy was required to confirm complete response after week 12 and at the end-of-treatment visit for the induction period in patients who had bone marrow involvement at screening.

For pharmacokinetic analyses, blood samples were collected before study drug infusion and 1 h after the end of the study drug infusion at each cycle during the induction period. Five further samples were collected during cycle 4 of the induction period, at the end of study drug infusion, and 24 h, 168 h, 336 h, and 504 h after the start of infusion. Blood samples for B-cell kinetics were collected before study drug infusion at each cycle during the induction period, 1 h after the end of infusion during cycle 1, and at the end-of-treatment visit for the induction period. Analyses of blood samples for routine laboratory parameters, immunoglobulins (IgM, IgG, and IgA), anti-drug antibodies, and neutralising antibodies were also done throughout the study. An enhanced chemiluminescence immunoassay method was used to measure anti-drug antibodies. Neutralising antibodies were measured using a complement-dependent cytotoxicity assay developed by Celltrion, Incheon, South Korea.

Outcomes

Each part of the study assessed one of two primary objectives. For part 1 of the study, the primary objective was to show equivalent pharmacokinetics in the pharmacokinetic subset, as assessed by two primary endpoints: area under the serum concentration–time curve at steady state (AUCτ) and maximum serum concentration at steady state (C_{maxSS}) at cycle 4 (week 9–12) of the induction period. For part 2, the primary objective was to measure non-inferior efficacy in the intention-to-treat (ITT) population, in terms of the proportion of patients who had an overall response (the proportion of patients who had complete response plus unconfirmed complete response plus partial response) derived by best overall response over 24 weeks of the induction period, according to 1999 International Working Group (IWG) criteria.[15] The IWG 1999 criteria were selected for this study, rather than the revised 2007 criteria that incorporate PET-CT imaging, because PET-CT equipment is not readily available or not used as a routine diagnostic method in many participating countries. Response was assessed centrally at baseline and weeks 12 and 24 by the independent review committee for reporting purposes and at a local level for confirmation of eligibility and treatment practice.

Secondary pharmacokinetic endpoints for part 1 included maximum serum concentration (C_{max}), trough serum concentration (C_{trough}), average concentration (C_{av}), time to maximum serum concentration (T_{max}), volume of distribution at steady state (V_{ss}), total clearance, terminal elimination half-life ($T_{1/2}$), mean residence time (MRT), peak-to-trough fluctuation ratio (PTF), and terminal elimination rate constant (λ). Secondary efficacy endpoints for part 2 included progression-free survival, time to progression, time to treatment failure, response duration, disease-free survival, and overall survival. These data are planned for separate publication following availability of long-term follow-up data.

Safety endpoints included incidence and type of adverse events, serious adverse events, and adverse events of special interest, such as incidence of infection or progressive multifocal leukoencephalopathy, concomitant medications, hypersensitivity (via vital signs monitoring including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature), physical examination findings, vital signs measurements, clinical laboratory analyses, chest x-ray, electrocardiograph findings, immunogenicity testing, immuglobulin testing, and tuberculosis assessment. Adverse events reported here are those that were not present before exposure to study treatment or those already present that worsened in intensity or frequency after exposure to study treatment.

Statistical analyses

We analysed pharmacokinetics in the pharmacokinetic subset; we analysed efficacy, pharmacodynamics, and safety, in the all randomised patient population, which included all patients in the pharmacokinetic subset.

134 patients were required to be enrolled into the study and randomised to receive CT-P10 (67 patients) or rituximab (67 patients) to obtain 116 evaluable patients (58 patients per treatment group), assuming a 13% dropout rate. From historical studies,[8,16] we estimated the variability in proportion of patients with an overall response with rituximab to be between 81% and 88% after up to eight cycles of treatment. At a non-inferiority threshold of –7% the study had at least an 80% power (at the lowest estimated historical threshold [81%]) to detect treatment differences with the specified number of patients in this study. However, with hindsight, this protocol-specified one-sided test did not adequately control the false positive rate, which reached the 2·5% significance level when the true difference in overall response was –21·3% or less, or –18·9% or less with 5% significance level. Consequently, we applied a conventional statistical non-inferiority test using a CI approach using the exact binomial CI for the difference in overall response between treatment groups. Here, we claimed non-inferiority if the one-sided 97·5% CI lay on the positive side of the –7% margin, using a one-sided test done at the 2·5% significance level.

We also estimated a statistical non-inferiority margin based on the effect size of rituximab. In an RCT[2] comparing patients treated with rituximab plus CVP versus CVP alone, the proportion of patients who had an overall response was 131 (81%) of 162 patients treated with rituximab plus CVP and 90 (57%) of 159 patients treated with CVP alone. The 95% CI of the difference in overall

response between groups was 0·145–0·341. The post-hoc statistical non-inferiority margin was estimated as –7·25% preserving 50% of the effectiveness of rituximab based on the one-sided 97·5% CI of the difference in overall response. Consequently, the protocol-specified non-inferiority margin of –7% also met the non-inferiority margin estimated based on the effect size of rituximab.

Overall response during the induction period was defined as the proportion of patients with a best overall response of complete response, unconfirmed complete response, or partial response. The best overall response was the best response recorded from randomisation until progressive disease, start of new anticancer therapy, end of induction period, or death, whichever came first. We repeated supportive efficacy analyses using the ITT population and in a predefined analysis of antibody-negative subsets of the efficacy and ITT populations. The ITT population comprised all patients enrolled and randomised, regardless of whether any study treatment was received.

We also did a sample size calculation for the pharmacokinetic subset. Based on 90% power using a two one-sided test approach[17] assuming a 5% significance level, 102 patients (51 patients per treatment group) were required to assess pharmacokinetic equivalence of CT-P10 and rituximab. Allowing for a 15% dropout rate, we estimated 120 patients were needed for randomisation. We analysed the pharmacokinetic primary endpoints of AUCτ and C_{maxSS} in patients who received all full doses of study drug up to week 12 (pharmacokinetic population), excluding outliers as determined by robust regression outlier testing. We calculated pharmacokinetic parameters by standard non-compartmental methods (linear trapezoidal rule) using Phoenix WinNonLin (version 6.4). Concentrations of less than the lower limit of quantification at baseline were set to zero. Concentrations of less than the lower limit of quantification after study drug exposure were set to the lower limit of quantification. We used an analysis of covariance (ANCOVA) on natural log-transformed AUCτ and C_{maxSS} values, with treatment as fixed effect and country, gender, race, ECOG performance status score, and FLIPI score (0–2 *vs* 3–5) at baseline fitted as covariates. We calculated geometric means and ratio of geometric means by back-transforming the least squares means of the log-transformed values of AUCτ and C_{maxSS}, and we produced 90% CI of the ratio of geometric least squares means of the two treatments. Equivalence was shown if the 90% CIs for the modelled ratio of CT-P10 to rituximab in AUCτ and C_{maxSS} were within the bounds of the equivalence margin of 80% and 125%. We did supportive analyses in the phamacokinetic population, including outliers, and in patients testing negative for anti-drug antibodies (including and excluding outliers).

We included all patients that received at least one dose of study drug (full or partial) in the safety population. We did pharmacodynamic analyses in the pharmacodynamic population (all patients who received at least one full dose of study drug [CT-P10 or rituximab] with at least one post-treatment pharmacodynamic result and who had no major protocol deviation relevant to the pharmacodynamic endpoint).

We did all statistical analyses using SAS software (version 9.1.3 or higher). We described continuous data using descriptive statistics. We summarised categorical data, including the primary efficacy endpoint, using patient counts and percentages.

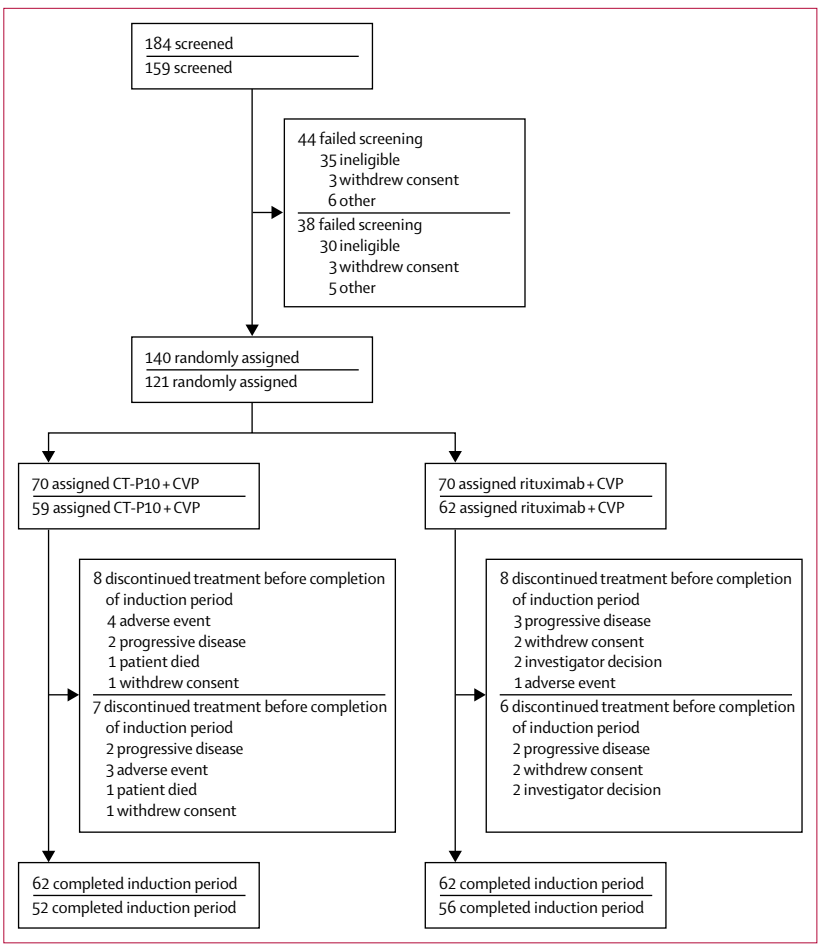

***Figure 1*: Patient disposition of the pharmacokinetic subset and all randomised patients**
Text above the line shows all randomised patients (all patients in the pharmacokinetic subset, plus additional recruits); text below the line shows the pharmacokinetic subset. Six patients (two patients from the CT-P10 group, four patients from the rituximab group) from a study site that was found to be non-compliant with good clinical practice were excluded from all analyses and study populations and are not included in the patient disposition figure. CVP=cyclophosphamide, vincristine, and prednisone.

Role of the funding source

The sponsor was involved in conception and design of the study and in data collection, analysis, and interpretation. All authors, including employees of the sponsor, participated in manuscript development. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication. SJL, SYL, and YJB had access to the raw data.

	Pharmacokinetic subset		All randomised patients	
	CT-P10 (n=59)	Rituximab (n=62)	CT-P10 (n=70)	Rituximab (n=70)
Age	54·0 (44–67)	58·5 (47–66)	57·0 (45–66)	58·5 (47–66)
Sex				
Female	33 (56%)	32 (52%)	40 (57%)	37 (53%)
Male	26 (44%)	30 (48%)	30 (43%)	33 (47%)
Race				
White or Caucasian	42 (71%)	49 (79%)	51 (73%)	52 (74%)
Asian	11 (19%)	10 (16%)	11 (16%)	13 (19%)
Other	6 (10%)	3 (5%)	8 (11%)	5 (7%)
FL grade at screening*				
Grade 1	18 (31%)	18 (29%)	21 (30%)	20 (29%)
Grade 2	31 (53%)	29 (47%)	36 (51%)	34 (49%)
Grade 3a	9 (15%)	15 (24%)	12 (17%)	16 (23%)
Ann Arbor principal staging at screening				
Stage III	17 (29%)	33 (53%)	21 (30%)	36 (51%)
Stage IV	42 (71%)	29 (47%)	49 (70%)	34 (49%)
FLIPI score at screening				
1	7 (12%)	5 (8%)	8 (11%)	6 (9%)
2	25 (42%)	20 (32%)	25 (36%)	21 (30%)
3	19 (32%)	26 (42%)	23 (33%)	30 (43%)
4	6 (10%)	11 (18%)	10 (14%)	12 (17%)
5	2 (3%)	0	4 (6%)	1 (1%)
ECOG performance status at screening				
0	37 (63%)	42 (68%)	44 (63%)	47 (67%)
1	21 (36%)	19 (31%)	25 (36%)	22 (31%)
2	1 (2%)	1 (2%)	1 (1%)	1 (1%)
Bone marrow involvement at screening	40 (68%)	28 (45%)	45 (64%)	33 (47%)
Bulky disease				
>7 cm	10 (17%)	12 (19%)	11 (16%)	14 (20%)
≤7 cm	49 (83%)	50 (81%)	59 (84%)	56 (80%)
Baseline lesion SPD (mm²)	3431·5 (1751·0–5719·2)	3463·7 (2227·5–5355·5)	3606·2 (1828·3–5471·0)	3463·7 (2182·4–5355·5)
LDH (U/L)				
Mean	286·5 (203·4)	258·7 (146·7)	291·7 (198·6)	259·5 (145·6)
Median	223·0 (175·0–319·0)	217·0 (174·0–269·0)	226·0 (177·0–319·0)	217·0 (170·0–269·0)
>UNL	14 (23·7)	17 (27·4)	21 (30·0)	20 (28·6)
≤UNL	45 (76·3)	44 (71·0)	49 (70·0)	49 (70·0)
B2 microglobulin (mg/L)				
Mean	2·8 (1·5)	3·0 (2·0)	2·9 (1·5)	3·1 (1·9)
Median	2·4 (1·9–3·2)	2·5 (1·9–3·2)	2·5 (1·9–3·4)	2·5 (2·0–3·4)
Haemoglobin (g/dL)				
Mean	12·9 (1·7)	13·0 (1·5)	12·9 (1·8)	13·0 (1·5)
Median	13·0 (11·6–14·2)	13·1 (12·3–13·9)	12·8 (11·6–14·2)	13·1 (12·3–14·1)
Median B-cell counts (cells per µL)	93 (57·0–216·0)	60 (31·0–139·0)	93 (55·0–216·0)	62 (31.0-139.0)

Data are median (IQR), n (%), or mean (SD), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. FL=follicular lymphoma. FLIPI=Follicular Lymphoma International Prognostic Index. ITT=intention-to-treat. SPD=sum of the product of the perpendicular diameters. LDH=lactate dehydrogenase. UNL=upper normal limit. *Data missing for one patient in the CT-P10 treatment group.

***Table 1*: Baseline patient demographics and disease status (ITT population)**

Results

This study was conducted between July 28, 2014 (when the first patient was randomised), and June 27, 2016 (the end of the induction period for the last patient). 140 patients were enrolled between July 28, 2014, and Dec 29, 2015. In part 1 of the study, 121 patients were enrolled and randomised to receive CT-P10 (n=59) or rituximab (n=62; figure 1). The number of patients randomised at each study centre is in the appendix (pp 3,4). 13 patients discontinued study treatment before

completion of the induction period, with eight patients discontinuing before completion of cycle 4. In part 2 of the study, 140 patients, including all patients from the pharmacokinetic subset, were randomised to CT-P10 (n=70) or rituximab (n=70) treatment groups (figure 1). 16 patients (including the 13 patients already described) discontinued study treatment before completion of the induction period. Six patients (four patients from the CT-P10 group and two patients from the rituximab group) were also excluded from the efficacy population, due either to non-compliance with eligibility (three patients from the CT-P10 group) criteria or because efficacy was not assessed in these patients (one patient from the CT-P10 group and two patients from the rituximab group).

Demographic characteristics were similar between treatment groups (table 1). At screening, all patients were Ann Arbor stage III (57 [41%] of 140) or stage IV (83 [59%] of 140). Bone marrow involvement was reported for 78 (56%) of 140 total patients; 45 (64%) of 70 patients in the CT-P10 group and 33 (47%) of 70 patients in the rituximab group. Approximately 30% of patients in the study had low-tumour-burden follicular lymphoma and 70% had a high tumour burden, according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. Patients with low tumour burden represented 30% of the total population, and were treated the same as other patients over the duration of the study period.

All patients except eight in each group were followed for 170 days (6 months; IQR 169–177 days in the CT-P10 group and 169–178 days in the rituximab group). Mean relative dose intensity of study drug up to week 24 was similar between treatment groups (97·7% [SD 4·4] for CT-P10 and 98·3% [2·7] for rituximab), as was that of combination therapy (cyclophosphamide, 97·7% [4·2] and 98·4% [2·6]; vincristine, 96·2% [8·6] and 96·9% [6·1]; prednisone or prednisolone, 97·7% [4·5] and 97·1% [4·0]).

The primary efficacy endpoint, the proportion of patients who achieved an overall response as judged by a central independent review committee, was 64 (97%) of 66 patients in the CT-P10 treatment group and 63 (93%) of 68 patients in the rituximab treatment group (efficacy population; table 2). The difference in the proportion of patients who achieved an overall response between the two treatment groups (calculated using percentages rather than rounded values) was 4·3% (one-sided 97·5% CI –4·25%) and lay on the positive side of the predefined non-inferiority margin using a protocol-specified point estimate difference of –7%. A similar result was observed in the ITT population (table 2). With respect to the conventional statistical non-inferiority test using the CI approach with the exact binomial CI for the difference of the proportion of patients who achieved an overall response between treatment groups, the one-sided 97·5% CI lay on the positive side of the –7% non-inferiority margin (–4·25% in the efficacy population and –3·41% in the ITT population). Therefore, the predefined non-inferiority criterion was met with both the protocol-specified point estimate difference approach and the conventional statistical non-inferiority test (CI approach) with a 2·5% significance level. The proportion of patients who achieved an overall response based on local assessment was not statistically different between treatment groups; the difference in overall response was 8·7% (97·0% for CT-P10 and 88·2% for rituximab; 95% CI –8·7 to 25·3) in the efficacy population and 10·0% (97·5% for CT-P10 and 85·7% for rituximab; 95% CI, –7·3 to 26·8) in the ITT population.

Based on evaluation by the independent review committee, the proportion of patients who achieved an overall response in the antibody-negative subset of the

	CT-P10	Rituximab	Difference (one-sided 97·5% CI)
Efficacy population	n=66	n=68	..
Overall response*	64 (97%)	63 (93%)	4·3% (–4·25)
Complete response	20 (30%)	15 (22%)	..
Unconfirmed complete response	6 (9%)	8 (12%)	..
Partial response	38 (58%)	40 (59%)	..
Stable disease	1 (2%)	2 (3%)	..
Relapsed disease or progressive disease	1 (2%)	2 (3%)	..
Unable to assess†	0	1 (2%)	..
ITT population	n=70	n=70	..
Overall response*	67 (96%)	63 (90%)	5·7% (–3·41)
Complete response	21 (30%)	15 (21%)	..
Unconfirmed complete response	6 (9%)	8 (11%)	..
Partial response	40 (57%)	40 (57%)	..
Stable disease	1 (1%)	2 (3%)	..
Relapsed disease or progressive disease	1 (1%)	2 (3%)	..
Unable to assess†	0	1 (1%)	..
Missing‡	1 (1%)	2 (3%)	..

Except where indicated otherwise, data are N or n (%) of patients. Tested in the efficacy population. ITT=intention-to-treat. *Complete response plus unconfirmed complete response plus partial response. †Unable to assess category included a patient who did not meet the minimum duration (8 weeks) for best overall response. The patient was evaluated as having partial response at end of treatment visit 1 (after 49 days from randomisation). ‡Missing cases included patients who had no efficacy assessment results at post-treatment visits.

***Table 2*: Proportion of patients who achieved overall response during the induction period—central independent review (best overall response)**

	Patients	Geometric least squares mean	Ratio (%) of geometric least squares means	90% CI of the ratio
AUC_{tau} (h·µg/mL)				
CT-P10	50	41 002·43	102·25%	94·05–111·17%
Rituximab	56	40 099·08	..	..
C_{maxSS} (µg/mL)				
CT-P10	53	256·19	100·67%	93·84–108·00%
Rituximab	56	254·49	..	..

Data are from the pharmacokinetic population excluding outliers (as determined by robust regression outlier testing). For the primary pharmacokinetic endpoint, outliers were identified by a robust regression model (95% CI). AUC_{tau}=area under the serum concentration–time curve at steady state. C_{maxSS}=maximum serum concentration at steady state.

***Table 3*: Pharmacokinetic primary endpoints**

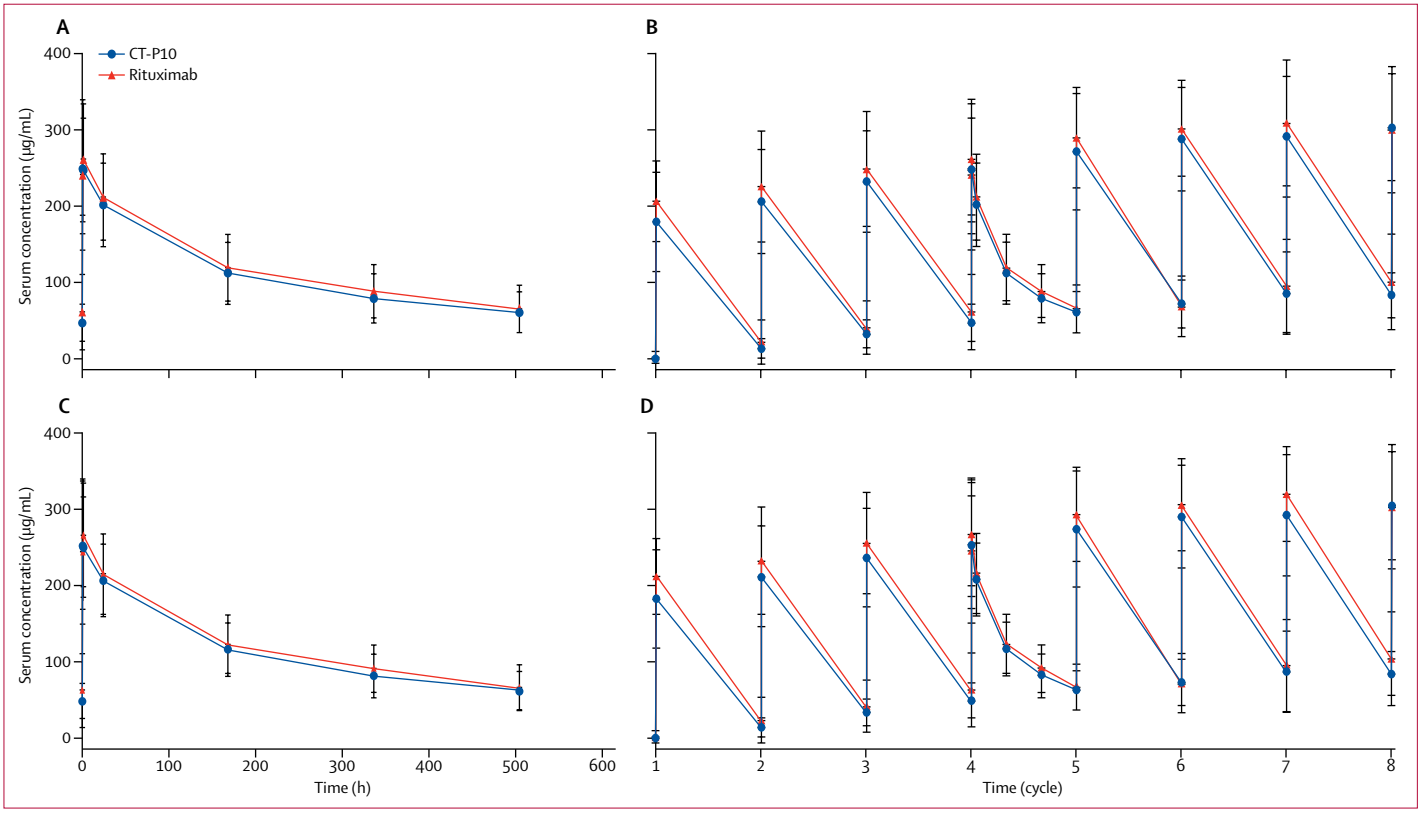

***Figure 2*: Serum concentration of CT-P10 and rituximab versus time**

Data are mean (±SD). Analyses are in the pharmacokinetic population (n=121; A, B) and the antibody-negative subset of the pharmacokinetic population (n=111; C, D). Data for cycle four is shown in A and C.

efficacy population was 61 (98%) of 62 patients in the CT-P10 treatment group and 61 (94%) of 65 patients in the rituximab treatment group (difference in overall response 4·5%, 95% CI –12·8 to 21·9). No patients tested positive for bone marrow involvement at any post-treatment visit after having tested negative at baseline. Among 78 patients (45 patients in the CT-P10 group and 33 patients in the rituximab treatment group) who tested positive at baseline, 39 patients tested negative at post-treatment visits (22 patients in the CT-P10 treatment group and 17 patients in the rituximab treatment group); no differences were found between the two treatment groups in the ITT population. After the induction period, B-symptoms were present in only one patient (CT-P10 treatment group), who was assessed as having a partial response.

The pharmacokinetics of CT-P10 and rituximab were equivalent because 90% CIs for the ratio of geometric least squares means of both AUCτ and C_{maxSS} were within the bioequivalence margin of 80–125%. The ratio of geometric least squares means (CT-P10 to rituximab) was 102·25% (90% CI 94·05–111·17) for AUCτ and 100·67% (93·84–108·00%) for C_{maxSS} (table 3). Patients considered outliers were excluded from the pharmacokinetic primary analysis. For AUCτ, seven patients (five in the CT-P10 treatment group and two in the rituximab treatment group), and for C_{maxSS}, four patients (two patients in each treatment group) were defined as outliers, as determined by robust regression outlier testing. The 90% CIs of the ratio of geometric least squares means for primary endpoints in the pharmacokinetic population including outliers, and also in the pharmacokinetic antibody-negative subset (with outliers excluded and included), were also contained within the equivalence margin of 80–125% (appendix p 6). At cycle 4 (week 9–12) of the induction period, mean serum concentrations of study drug at steady state were similar for the CT-P10 and rituximab treatment groups (figure 2A) and at each time point throughout the induction period (figure 2B). Mean serum concentrations were also similar for the two treatment groups in the antibody-negative subset of the pharmacokinetic population, both at steady state (figure 2C) and throughout the induction period (figure 2D). Steady state values for all secondary pharmacokinetic endpoints at cycle 4 (week 9–12) were similar for the CT-P10 and rituximab treatment groups (appendix p 7). No differences in secondary pharmacokinetic endpoints at each cycle between treatment groups were noted (appendix p 7).

B-cell kinetics over the 24 weeks of the induction period were similar in the two treatment groups. The median number of B cells decreased to the lower limit of quantification (20 cells per µL) 1 h after the end of

infusion at cycle 1 and remained at the lower limit of quantification at each subsequent cycle, up to and including cycle 8 (appendix p 9).

Treatment-emergent adverse events were reported for 58 (83%) of 70 patients in the CT-P10 group and 56 (80%) of 70 patients in the rituximab group (table 4), including one patient in the CT-P10 group who had grade 5 tumour lysis syndrome. Adverse events considered by the investigator to be associated with study drug were reported for 37 (53%) patients in the CT-P10 group and 34 (49%) patients in the rituximab group (table 5). The most frequently reported study drug-related adverse events were neutropenia and infusion-related reactions in the CT-P10 treatment group (15 [21%] patients for both), and infusion-related reactions (17 [24%] patients) and neutropenia (five [7%] patients) in the rituximab group. Serious adverse events occurred in 16 (23%) patients in the CT-P10 group and nine (13%) patients in the rituximab group. All cases of serious adverse events that are associated with risk factors such as old age, use of immunosuppressants, diabetes mellitus, chronic obstructive pulmonary disease, or coronary artery disease were considered unrelated to the study drug by investigators. The proportion of patients who experienced at least one study drug-related serious adverse event was similar in the two treatment groups (six [9%] in the CT-P10 group and four [6%] in the rituximab group). Study drug-related serious adverse events included one abnormal liver function test and one case each of pneumonia, deep vein thrombosis, anaphylactic shock, and tumour lysis syndrome (CT-P10 group only), one case each of encephalitis and ileus (rituximab group only), neutropenia (one case each for CT-P10 and rituximab groups), one case of leukopenia (rituximab group only), and one case of pancytopenia (CT-P10 group only). Serious adverse events considered unrelated to study drug included two cases of pneumonia, and one case each of anaemia, angina pectoris, atrial fibrillation, constipation, small intestinal perforation, cholecystitis, abdominal infection, campylobacter gastroenteritis, post-procedural fistula, hypoalbuminaemia, hypocalcaemia, hypomagnesaemia, pleural effusion, and pulmonary embolism (CT-P10 group only); one case each of diarrhoea, pyrexia, subdural haematoma, and thrombophlebitis (rituximab group only); and four cases of neutropenia (three patients in the CT-P10 group and one patient in the rituximab group), three cases of chronic obstructive pulmonary disease (two patients in the CT-P10 group and one patient in the rituximab group), and two cases of lower respiratory tract infection (one patient in each treatment group). Full details of all serious adverse events are in the appendix (p 10). Study drug-related adverse events due to infection were reported in six (9%) patients in the CT-P10 group and nine (13%) patients in the rituximab group.

The most frequently reported adverse events due to infection (any cause) in the CT-P10 group were upper respiratory tract infection, lower respiratory tract infection, and pneumonia (each present in five [7%] patients). The most frequently reported study drug-related adverse events due to infection (any cause) in the rituximab group was upper respiratory tract infection (12 [17%] patients) and urinary tract infection (four [6%] patients). Five patients (four [6%] patients in the CT-P10 group and one [1%] patient in the rituximab group) had study drug-related adverse events that led to permanent study drug discontinuation; all patients had existing risk factors. In the case of CT-P10, these events were infusion-related reaction (one [1%] patient with previous incidences of anaphylactic shock, who was anti-drug antibody positive and tested positive for neutralising antibodies at cycle 4), angina pectoris (one [1%] patient with a history of paroxysmal atrial fibrillation and left ventricular hypertrophy), post-procedural fistula (one [1%] patient with a history of large mass excision and small bowel section), and an abnormal liver function test (one [1%] patient with existing steatosis). For rituximab, tuberculosis occurred in one (1%) patient with a history of the disease.

	CT-P10 (n=70)			Rituximab (n=70)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Abdominal pain	6 (9%)	0	0	10 (14%)	0	0
Alopecia	10 (14%)	0	0	5 (7%)	0	0
Back pain	1 (1%)	0	0	7 (10%)	0	0
Constipation	12 (17%)	0	0	9 (13%)	0	0
Hypocalcaemia	2 (3%)	0	1 (1%)	1 (1%)	0	0
Hypokalaemia	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0
Ileus	0	0	0	0	0	1 (1%)
Infusion-related reaction	15 (21%)	2 (3%)	0	17 (24%)	0	0
Nausea	7 (10%)	0	0	5 (7%)	0	0
Neuropathy (peripheral)	10 (14%)	0	0	11 (16%)	1 (1%)	0
Neutropenia	12 (17%)	15 (21%)	5 (7%)	8 (11%)	7 (10%)	5 (7%)
Paraesthesia	3 (4%)	1 (1%)	0	8 (11%)	0	0
Pneumonia	1 (1%)	4 (6%)	0	1 (1%)	0	0
Upper respiratory tract infection	5 (7%)	0	0	12 (17%)	0	0

Data are n (%) of patients. Adverse events are shown for grade 1–2 in 10% or more of patients, grade 3 in 5% or more of patients, or grade 4 (all events).

***Table 4*: Summary of treatment-emergent adverse events**

	CT-P10 (n=70)	Rituximab (n=70)
Number of patients with ≥1 study drug-related adverse events		
Any adverse event	37 (53%)	34 (49%)
Grade ≥4 adverse event	5 (7%)	4 (6%)
Serious adverse event	6 (9%)	4 (6%)
Study drug-related adverse events due to infection	6 (9%)	9 (13%)
Study drug-related adverse events reported for ≥5% patients in either treatment group		
Neutropenia	15 (21%)	5 (7%)
Asthenia	2 (3%)	4 (6%)
Fatigue	1 (1%)	4 (6%)
Infusion-related reaction	15 (21%)	17 (24%)

***Table 5*: Summary of study drug-related adverse events**

One death was reported after the first cycle in the induction period (CT-P10 group). Cause of death was reported as tumour lysis syndrome, although the evidence was insufficient regarding relevant laboratory measurements to confirm this diagnosis. Neither allopurinol nor hydration were administered as measures to prevent tumour lysis syndrome in this patient despite the patient having poor kidney function at baseline. No cases of hepatitis B reactivation or progressive multifocal leukoencephalopathy were reported.

Most patients had negative results in anti-drug antibody tests during the induction period. Five patients (3 [4%] patients in the CT-P10 group and two [3%] patients in the rituximab group) had at least one positive result in anti-drug antibody tests at post-treatment visits during the induction period. All patients with an anti-drug antibody-positive result at post-treatment visits had positive results in neutralising antibody tests, with the exception of one patient in the CT-P10 treatment group. Mean immunoglobulin levels were decreased from baseline throughout the induction period, with no notable differences between treatment groups. For other safety assessments, including vital signs, electrocardiogram, and physical examination, there were no notable differences between the two treatment groups during the induction period.

Discussion

In this study we aimed to assess whether CT-P10 had non-inferiority of efficacy and equivalence of pharmacokinetics compared with rituximab, when used in combination with CVP in patients with newly diagnosed advanced-stage follicular lymphoma. The primary endpoint of part 2 of the study (the proportion of patients who achieved an overall response using best overall response) shows that CT-P10 is not inferior to rituximab with respect to efficacy, because the non-inferiority criterion was met using both the protocol-specified point estimate difference approach and the conventional statistical non-inferiority test (CI approach) with a 2·5% significance level. Supportive analyses revealed that the proportion of patients who achieved an overall response showed a similar result in the ITT population and the antibody-negative subset of the efficacy population. Efficacy data from both treatment groups in this study were consistent with those seen in previous studies: overall response of 74% up to four cycles[17] and 81–88% up to eight cycles.[2,16,18]

The primary endpoints for part 1 of the study (AUCτ and C_{maxSS} at cycle 4 of the induction period) were equivalent between the CT-P10 and rituximab groups, because the 90% CIs for the ratios of their geometric least squares mean values were within the predefined bioequivalence margins of 80–125%. These primary findings (in the pharmacokinetic population excluding outliers) were corroborated by supportive analyses that showed that these endpoints were also equivalent between CT-P10 and rituximab in the pharmacokinetic population including outliers and the pharmacokinetic antibody-negative subset (both including and excluding outliers). There were no notable differences in secondary pharmacokinetic endpoints during the induction period between the two treatment groups. Therapeutic drug concentrations were achieved in both treatment groups and pharmacokinetic data were broadly consistent with those previously reported for CT-P10 and rituximab in patients with follicular lymphoma.[19–21]

Pharmacodynamics, specifically B-cell counts, were similar between the CT-P10 and rituximab groups, and were consistent with previous findings in patients with rheumatoid arthritis.[8] At baseline, median B-cell counts were 93 cells per µL in the CT-P10 group and 62 cells per µL in the rituximab groups. These levels are in line with the range of B-cell counts observed in patients with non-Hodgkin lymphoma in a previous study[22] of CT-P10 involving rituximab (5–4272 cells per µL). Median B-cell counts decreased to the lower limit of quantification (20 cells per µL) in both treatment groups 1 h after the first infusion of the study drug and remained at the lower limit of quantification throughout the induction period.

The overall safety profile of CT-P10 observed in this study was consistent with the known profile of rituximab plus CVP chemotherapy[2] and no new or unexpected safety findings were observed. Of note, the number of patients with neutropenia related to study drug was 15 (21%) in the CT-P10 group and five (7%) in the rituximab group. Given that there were no notable treatment group differences in the magnitude of decreases in neutrophil count, the variation in the percentage of patients with neutropenia was probably driven by uneven distribution of baseline risk factors between treatment groups. Bone marrow involvement, which is associated with the development of neutropenia following chemotherapy,[23] affected more patients in the CT-P10 group (45 [64%] patients) than in the rituximab group (33 [47%] patients). Advanced disease stage has also been associated with an increased risk of neutropenia in patients with cancer undergoing chemotherapy,[24] and a higher proportion of patients receiving CT-P10 had stage IV disease (49 [70%] patients *vs* 34 [49%] patients). The percentage of patients who experienced infusion-related reactions or infections was similar between the two treatment groups and was consistent with the range reported in historical data from the pivotal innovator rituximab trials (infusion-related reactions, range 22–71%; infections, range 30–55%).[1] No cases of progressive multifocal leukoencephalopathy were reported in the study.

Because this study was designed to facilitate showing biosimilarity in compliance with the relevant regulatory guidelines, some additional considerations were included during study design; notably choice of chemotherapy and primary efficacy endpoint. In this study, CVP was selected as the chemotherapy regimen based on the literature

evidence, suitability of the regimen for the study's patient population, and clinical guidelines. A study by Marcus and colleagues[2] in 2005 clearly showed that the addition of rituximab to CVP has a significant incremental effect on efficacy, with a 24% increase in the proportion of patients who achieved an overall response and 30% increase in rate of complete response.[2] Thus, we considered that there was sufficient evidence that this model displays adequate assay sensitivity. Additionally, CVP is considered to be relatively mild compared with chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) or bendamustine-containing and fludarabine-containing regimens. 30% of patients in this study were considered to have low-tumour-burden follicular lymphoma, according to GELF criteria, and therefore a less aggressive therapy such as CVP might be more appropriate in these circumstances. Furthermore, investigators from the study centres deemed rituximab plus CVP to be an appropriate treatment option for all patients enrolled into the study. Finally, a number of oncology guidelines continue to recommend rituximab plus CVP as a first-line treatment option for follicular lymphoma, including those from the National Comprehensive Cancer Network and the National Institute for Health and Care Excellence.[6,25]

The proportion of patients who achieved an overall response was used as the primary efficacy endpoint in this study in line with EMA and FDA guidance.[13,26] Compared with progression-free survival or overall survival, which are more commonly used for therapeutic studies of novel agents, the proportion of patients who achieved an overall response is considered a sufficiently sensitive and appropriate primary endpoint for biosimilar oncology in circumstances in which a large treatment effect is expected, such as that observed with rituximab. Survival data will be assessed as a secondary endpoint in a separate report of this study.

The proportion of patients who achieved an overall response in this study was slightly higher than that reported by Marcus and colleagues[2] (93% *vs* 81%), which might be attributed to the lower proportion of patients with bulky disease in this study (20% *vs* 39%).[2] However, because patient disease status was comparable between treatment arms in this study, we do not think the lower proportion of patients with bulky disease affects our study findings. One potential limitation of this study is that although tissue for pathological diagnosis was reviewed by local assessment for eligibility evaluation and by central independent review for reporting purposes, some patients did not have an appropriate specimen to do this central review process. The main limitation of this study is its relatively short follow-up period (24 weeks). However, this report only intended to present the primary results following the induction period. The study is ongoing and patients with a response after the induction period will receive maintenance therapy up to a maximum of 12 cycles, with CT-P10 or rituximab administered every 2 months for a maximum of 2 years. Patients will be followed for up to 3 years from the first day of the first treatment cycle of the last patient to collect longer-term data on the comparability of CT-P10 to rituximab. These longer term data should include robust endpoints that are considered important for assessing therapeutic methods in follicular lymphoma, such as progression-free survival and overall survival. Although this longer-term data is vital for analysis of these endpoints, we recognise that the study was not powered to compare survival parameters between the two treatment arms. In terms of study strengths, this trial was powered to show the pharmacokinetic equivalence of CT-P10 and rituximab in the clinical setting and is, to our knowledge, the first phase 3 trial in patients with haematological malignancies to do so.

Studies with CT-P10—including this trial—have confirmed comparable efficacy and pharmacokinetics to rituximab in both inflammatory disease (rheumatoid arthritis) and haematological malignancy (follicular lymphoma), providing strong support for the use of CT-P10 in these indications. Although, according to preliminary reports,[27,28] other rituximab biosimilars in development have shown similarity to rituximab in terms of efficacy, pharmacokinetics, and pharmacodynamics, this is to our knowledge the first rituximab biosimilar phase 3 trial in patients with cancer to be published in full.

In this multinational, randomised, parallel-group, phase 3 study, CT-P10 showed non-inferiority of efficacy, equivalence of pharmacokinetics, and comparable pharmacodynamics to rituximab up to week 24 in patients with previously untreated advanced-stage follicular lymphoma. CT-P10 was well tolerated, and the safety and immunogenicity profiles of CT-P10 were comparable to those of rituximab over the eight-cycle induction period. CT-P10 might be a therapeutic option for advanced-stage follicular lymphoma, and possibly other B-cell haematological malignancies, in place of rituximab. This phase 3 trial is ongoing, and longer-term data for patients with advanced-stage follicular lymphoma on maintenance therapy will be assessed when available.

Contributors

WSK, CB, MO, LWK, SJL, SYL, YJB, and BC were involved in conception and design of the study, acquisition of data, and the analysis and interpretation of data. WJ, J-MS, EZ, JSK, J-AH-R, AP, MV, RN, and DO were involved in the acquisition of data. All authors reviewed drafts of the manuscript and approved the final version.

Declaration of interests

SJL, SYL, and YJB are employees of Celltrion. BC, J-AH-R, LWK, and MO have received research funding from Celltrion during the conduct of this study. BC has also received personal fees from Celltrion, Roche, Pfizer, Mundipharma, Celgene, MorphoSys, Gilead, Novartis, and Takeda outside the submitted work. WJ has received research funding from Celltrion not related to the current study and research and personal fees from Sandoz Novartis, MorphoSys, and Roche outside the submitted work. LWK has received personal fees from Celltrion outside the submitted work. MO has received research funding from Symbio, and personal fees from Celltrion, Celgene, AstraZeneca, Takeda, Mundipharma, and Meiji Seika Pharma outside the submitted work.

CB, JSK, AP, DO, MV, RN, J-MS, WSK, and EZ declare no competing interests.

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