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Pharmacokinetic and Safety of CT-P10, a Biosimilar Candidate to the Rituximab Reference Product, in Patients with newly diagnosed Advanced Stage Follicular Lymphoma (AFL)

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Background: CT-P10 is a biosimilar candidate to the reference rituximab product, EU-approved MabThera® and US-licensed Rituxan®. CT-P10 has an identical amino acid sequence and highly similar physicochemical and in vitro functional properties to its reference drug. In patients with rheumatoid arthritis, CT-P10 has demonstrated compelling similarity in pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety and immunogenicity (Yoo DH *et al.*, 2013).

Objective: The goal of this study was to demonstrate PK similarity of CT-P10 to rituximab, each administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with newly diagnosed Advanced Follicular Lymphoma (AFL) (NCT02162771) (Kim WS *et al.*, 2015). The results of PK, PD, safety and immunogenicity up to Core Cycle 4 (12 weeks) are presented here from this ongoing study.

Methods: Patients with AFL were randomized 1:1 to receive infusion (375mg/m^2) of either CT-P10 or rituximab, at a 3-week interval, in combination with CVP. PK analysis was conducted in terms of AUC_{tau} and C_{max} at steady state, Core Cycle 4, as primary PK endpoints. Patients considered outliers as determined by robust regression outlier testing were excluded from the pharmacokinetic primary analysis.

Results: In total, 121 patients were randomly assigned to receive either CT-P10 (n=59) or rituximab (n=62) in combination with CVP. Result of CT-P10 PK at Core Cycle 4 was similar to that of rituximab. The ratios (90% CI) of geometric least square means (CT-P10 to rituximab treatment group) were 102.3% (94.1%-111.2%) for AUC_{tau} and 100.7% (93.8%-108.0%) for C_{maxSS} at Core Cycle 4. The 90% CIs of ratio of geometric LS means for both AUC_{tau} and C_{maxSS} were entirely contained within the equivalence margin of 80% to 125% (Table 1 and Figure 1). Mean serum concentrations of the study drug were highly similar for the 2 treatment groups at each time point (Core Cycle 1 to 4).

The B-cell kinetics was similar up to Core Cycle 4 in the 2 treatment groups. Median number of B-cells decreased to below the lower limit of quantification (LLoQ) (20 cells/μL) 1 hour after the end of infusion at Core Cycle 1 and remained below the LLoQ at each subsequent cycle, up to and including Core Cycle 4.

The proportion of patients with a positive anti-drug antibody up to Core Cycle 4 at post-treatment visits was similar between the 2 treatment groups; 3/59 (5.1%) patients and 2/62 (3.2%) patients in the CT-P10 and rituximab groups, respectively.

In addition, CT-P10 was well tolerated and the safety profile of CT-P10 up to Core Cycle 4 was similar to that of rituximab. The number of patients who experienced at least 1 treatment emergent adverse event (TEAE) was 43 (72.9%) patients and 41 (66.1%) patients in CT-P10 and rituximab treatment groups, respectively. The proportion of patients who experienced at least 1 treatment emergent serious adverse event considered by the investigator to be related to the study treatment was similar between the 2 treatment groups; 2/59 (3.4%) patients and 2/62 (3.2%) patients in the CT-P10 and rituximab groups, respectively. The frequencies of adverse events

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special interest (AESI) were similar between the 2 treatment groups (Table 2).

Table 1. Statistical Analysis of Rituximab Pharmacokinetic Primary Endpoints for Core Cycle 4 at Steady State: Pharmacokinetic Population

Parameter (Unit)	Treatment	n	Geometric Least Squares Mean	Ratio (%) of Geometric LS Means	90% Confidence Interval of the Ratio
AUC_{tau} (h × µg/mL)	CT-P10	50	41011	102.3	94.1-111.2
	Rituximab	56	40099		
C_{maxSS} (µg/mL)	CT-P10	53	256.19	100.7	93.8-108.0
	Rituximab	56	254.49		

Abbreviations: AUC_{tau}, area under the serum concentration-time curve at steady state; C_{maxSS}, maximum serum concentration at steady state.

Figure 1. Mean (±SD) Serum Concentration of Rituximab Versus Time for Cycle 4 at Steady State (Linear Scale): Pharmacokinetic Population

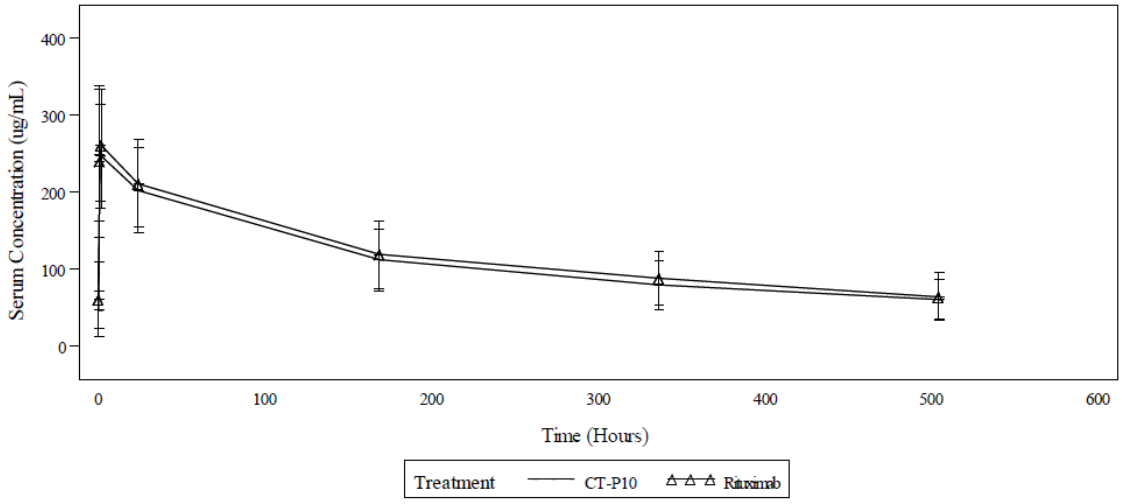

Table 2. The Incidence Rates of Adverse Events Special Interest: Safety Population

Adverse events special interest	CT-P10 (N=59)	Rituximab (N=62)	Total (N=121)
	Number(%) of Patients		
Infusion related reaction	15 (25.4)	13 (21.0)	28 (23.1)
Infection	12 (20.3)	13 (21.0)	25 (20.7)
Progressive multifocal leukoencephalopathy	0	0	0
Serious viral infection	0	0	0
Hepatitis B virus reactivation	0	0	0

Conclusion: This study demonstrated similarity of PK in terms of AUC_{tau} and C_{maxSS} between CT-P10 and rituximab in AFL patients. The B-cell kinetics and immunogenicity were comparable between the two treatment groups. CT-P10 was well tolerated with a safety profile comparable to that of rituximab up to and including Core Cycle 4 (12 weeks).