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Truxima: Biosimilar of Rituximab
(EMEA/H/C/004112)

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Introduction

- A biosimilar application of rituximab in the treatment of Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Rheumatoid arthritis (RA), Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA)

- Drug substance and drug product are manufactured by CELLTRION (Yeonsu-gu, Korea).

- Reference medicinal product MabThera® for intravenous (IV) use, which has been approved in the European Union (EU) in February 1998 (EMEA/H/C/000165)

Clinical studies

Protocol	Design	Objective(s)	Treatment	Status
CT-P10 1.1 (PK Similarity)	Phase 1, randomised (2:1), controlled, multicentre, 2-arm, parallel-group, double-blind study in patients with RA	**Primary:** To demonstrate similarity of PK in terms of $AUC_{0\text{-last}}$ and C_{max} between CT-P10 and MabThera® in patients with RA up to Week 24. **Secondary:** To evaluate additional PK variables, long-term efficacy, PD, overall safety, and biomarker up to Week 72. Tertiary: To evaluate additional PK variables (C_{min} and C_{trough}) in the 2nd course.	CT-P10 or MabThera® (1000 mg by IV infusion) co-administered with MTX (10-25 mg/week orally or parenterally) and folic acid (≥5 mg/week) up to 2 course of treatment. Each course consists of 2 infusions with a 2-week interval at Week 0 and 2. Randomised: 154 CT-P10: 103 MabThera®: 51	Completed
CT-P10 1.3 (Extension study to CT-P10 1.1)	Open-label, single-arm, maintenance study to demonstrate long-term efficacy and safety of CT-P10 in patients with RA who were treated with CT-P10 or MabThera® in Study CT-P10 1.1	To evaluate long term efficacy and safety of CT-P10 in patients with RA up to 104 weeks.	CT-P10 (1000 mg by IV infusion) co-administered with MTX (10-25 mg/week orally or parenterally) and folic acid (≥5 mg/week) up to 2 course of treatment; Each course consists of 2 infusions with a 2-week interval. Enrolled: 87 Received study drug treatment: 58 CT-P10 Maintenance: 38 CT-P10 Switch: 20	Completed
CT-P10 1.2 (Pilot Study)	Phase 1, open-label, multicentre, single-arm study in patients with DLBCL as second-line chemotherapy	**Primary:** To provide initial evidence of safety of CT-P10 after 2 cycles of treatment when administered with DHAP as the second-line therapy to patients with relapsed or	CT-P10 (375 mg/m^2 by IV infusion) co-administered with DHAP (dexamethasone [40 mg orally or IV], cytosine arabinoside [2000 mg/m^2 IV], cisplatin [100 mg/m^2 IV infusion]) up to 2 cycles during Induction	Study terminated due to recruitment difficulties Synoptic study

Clinical studies (2)

Protocol	Design	Objective(s)	Treatment	Status
CT-P10 3.2 (Therapeutic similarity)	Phase 3, randomised (1:1:1), controlled, multicentre, 3-arm, parallel-group, double-blind, prospective study in patients with RA	**Primary:** (Part 1) To demonstrate similarity of PK in terms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} of CT-P10 to Rituxan®, CT-P10 to MabThera® and Rituxan® to MabThera® over the first 24 weeks (Part 2) To demonstrate that CT-P10 is similar to reference products (Rituxan® and MabThera®)[1] in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by DAS28 (CRP) at Week 24 **Secondary:** To evaluate the additional efficacy, PK, PD, overall safety, and biomarkers of CT-P10 compared with Rituxan® and MabThera®	CT-P10 or Rituxan®/ MabThera® (1000 mg) administered by IV infusion. Each patient may receive 3 courses (2 courses in the Main Study Period and 1 course in the Extension Study Period) of treatment if the patient meets predefined safety criteria. MTX (10-25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week) will be co-administered. Part 1, 63 patients per each treatment group, total 189 planned Part 2, additional 86 patients for each CT-P10 and Rituxan® group, total 361 planned, including 189 patients from part 1.	Ongoing Estimated first CSR completion: 2Q/2016 (The study reports will include data on PK, PD, efficacy, safety, immunogenicity and biomarker.) Estimated final CSR completion: 4Q/2017
CT-P10 3.3 (PK similarity)	Phase 1/3 randomised (1:1), controlled, multicentre, parallel-group, double-blind study in patients with AFL	**Primary:** (Part 1) To demonstrate similarity in terms of PK as determined by AUC_{tau} and C_{maxSS} of CT-P10 to US-licensed Rituxan® (Part 2) To demonstrate non-inferiority of CT-P10 to Rituxan® in terms of efficacy as determined by clinical response according to the 1999 IWG criteria **Secondary:**	CT-P10 or Rituxan® (375 mg/m^2 IV infusion) with CVP (cyclophosphamide [750 mg/m^2 IV], vincristine [1.4 -2 mg/m^2, IV], and prednisone [40 mg/m^2, oral]) administered every 3 weeks up to 8 cycles during the Core Study Period. CT-P10 or Rituxan® administered every 2 months up to 12 cycles in the Maintenance Study Period. Part 1, 60 patients per each treatment	Ongoing Estimated first CSR completion: 2Q/2016 (The study reports will include data on PK, PD, safety, immunogenicity and biomarker.)

PK similarity (study 1.1)

Parameter	Treatment	N	Geometric Mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
PK population					
$AUC_{0\text{-last}}$ (day•µg/mL)[a]	CT-P10 1000 mg	96	7838.62	97.72	89.23 - 107.00
	MabThera 1000 mg	45	8021.86		
C_{max} (µg/mL)[a]	CT-P10 1000 mg	96	465.94	97.57	91.96 - 103.53
	MabThera 1000 mg	45	477.52		
$AUC_{0\text{-last}}$ (day•µg/mL)[b]	CT-P10 1000 mg	96	7859.29	96.90	88.10 - 106.58
	MabThera 1000 mg	45	8110.54		
C_{max} (µg/mL)[b]	CT-P10 1000 mg	96	465.76	95.77	89.40 - 102.60
	MabThera 1000 mg	45	486.32		

Abbreviations: $AUC_{0\text{-last}}$, area under the serum concentration time curve from the start of the first infusion to the last measurable concentration after the second infusion; C_{max}, maximum serum concentration; PK, pharmacokinetic; TNF, tumor necrosis factor.

Note: The primary PK endpoints were analyzed using an analysis of covariance model with treatment as a fixed effect and region and prior anti-TNF-α blocker status fitted as covariates. Point estimates (geometric means and ratio of geometric means) were calculated from back-transforming the least squares means of the natural log-transformed values of $AUC_{0\text{-last}}$. $AUC_{0\text{-last}}$ was natural log-transformed prior to analysis, and 90% CIs for the ratio of the geometric means of the 2 treatments were produced. The equivalence of pharmacokinetics between CT-P10 and MabThera was concluded if the 90% CIs for the test product to reference product ratios of geometric means were entirely contained within 80% to 125% for both $AUC_{0\text{-last}}$ and C_{max}.

[a] Concentration data considered as outliers from a PK perspective were excluded from the analysis for Patients 0209-1009, 0806-1001, and 0607-1004.

[b] Patients 0209-1009, 0806-1001, and 0607-1004 were included in this PK analysis.

PK similarity (study 3.2)

Parameter	Comparison	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
$AUC_{0\text{-last}}$ (h•µg/mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	62	163216.09	94.08	84.63 - 104.58
		Reference	59	173484.71		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	62	163216.09	101.84	91.77 - 113.01
		Reference	63	160266.18		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	59	173484.71	108.25	97.32 - 120.40
		Reference	63	160266.18		
$AUC_{0\text{-inf}}$ (h•µg/mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	59	163055.24	89.91	81.40 - 99.31
		Reference	56	181353.13		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	59	163055.24	98.91	89.77 - 108.97
		Reference	62	164855.33		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	56	181353.13	110.01	99.64 - 121.45
		Reference	62	164855.33		
C_{max} (µg/mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	62	377.83	88.99	82.40 - 96.10
		Reference	59	424.57		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	62	377.83	101.39	94.00 - 109.35
		Reference	63	372.65		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	59	424.57	113.93	105.45 - 123.09
		Reference	63	372.65		

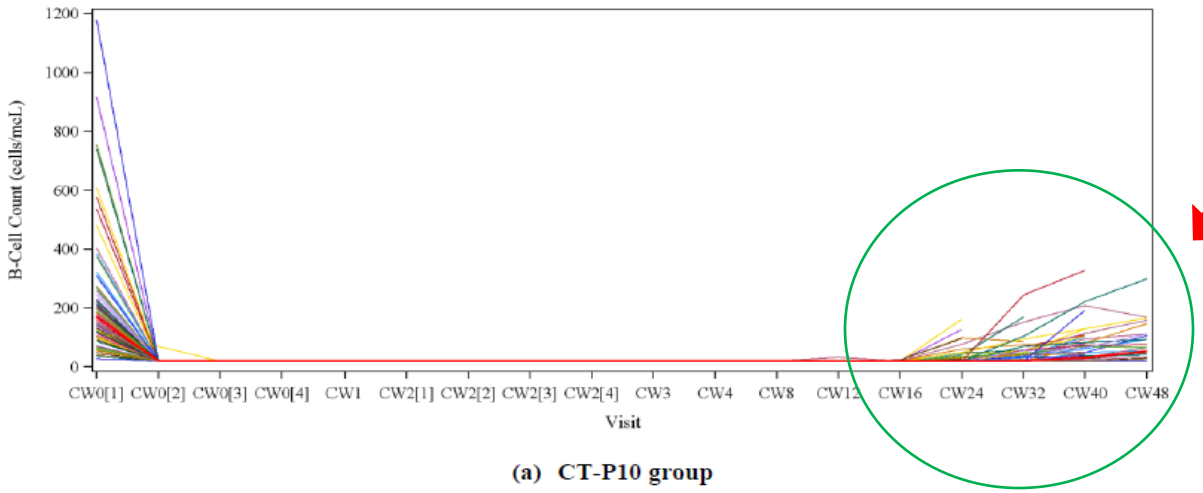
PK similarity (study 3.3)

Table 11-6 Statistical Analysis of Rituximab Pharmacokinetic Primary Parameters for Core Cycle 4 at Steady State (ANCOVA): Pharmacokinetic Population - Excluding Outliers

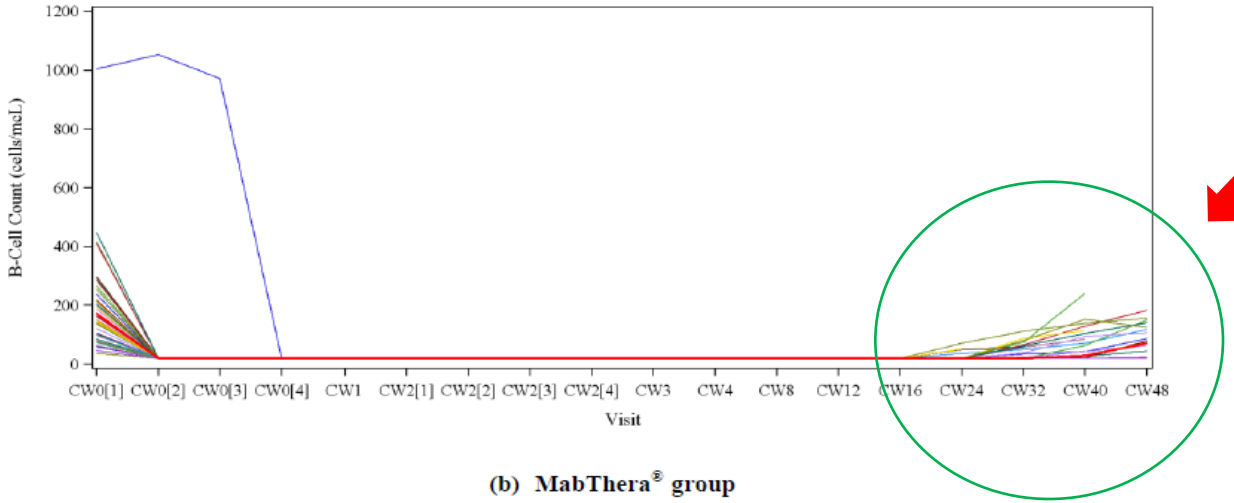
Parameter (unit)	Treatment	n	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% Confidence Interval of the Ratio
AUC_{tau} (h•µg/mL)	CT-P10	50	41011.08	102.27	94.08-111.18
	Rituxan	56	40099.22		
C_{maxSS} (µg/mL)	CT-P10	53	256.19	100.67	93.84-108.00
	Rituxan	56	254.49		

In the PK population including outliers, the ratio (90% CI) of geometric LS means (CT-P10 to Rituxan treatment group) was **95.32% (81.03%-112.14%)** and **101.38% (93.49%-109.94%)** for **AUCtau** and **CmaxSS**, respectively

PD similarity (Study 1.1)



(a) CT-P10 group



(b) MabThera® group

Source: Section 5.3.5.3 Figure 3.02
Note: The following time points where measured on the day of infusion: [1] Within 15 minutes before start of infusion [2] Within 15 minutes after infusion end [3] 60 +/- 15 minutes after infusion end [4] 24 hours after infusion end.
Red bold line indicates median value.
CW = Core Week

PD similarity (Study 1.1)

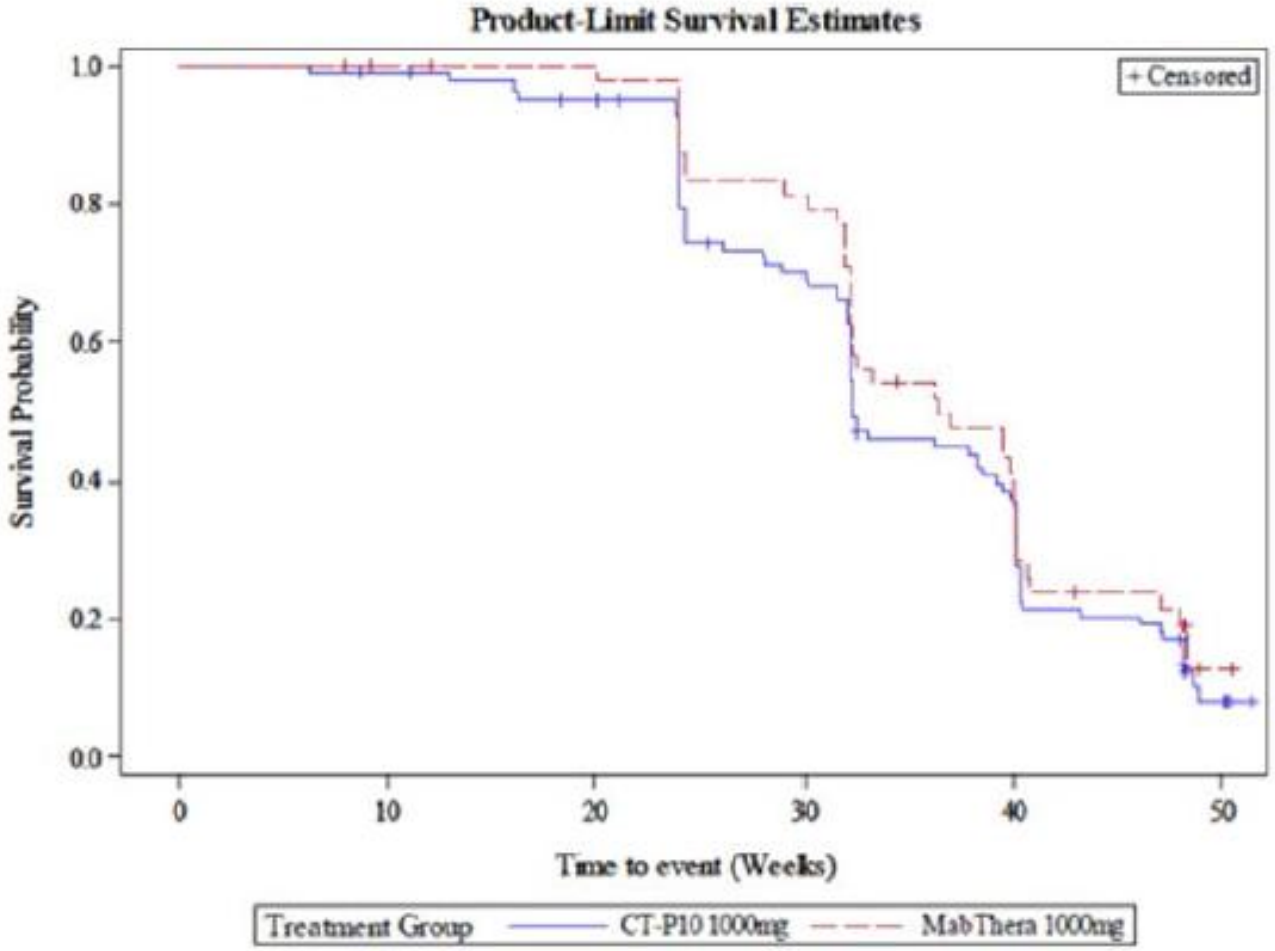
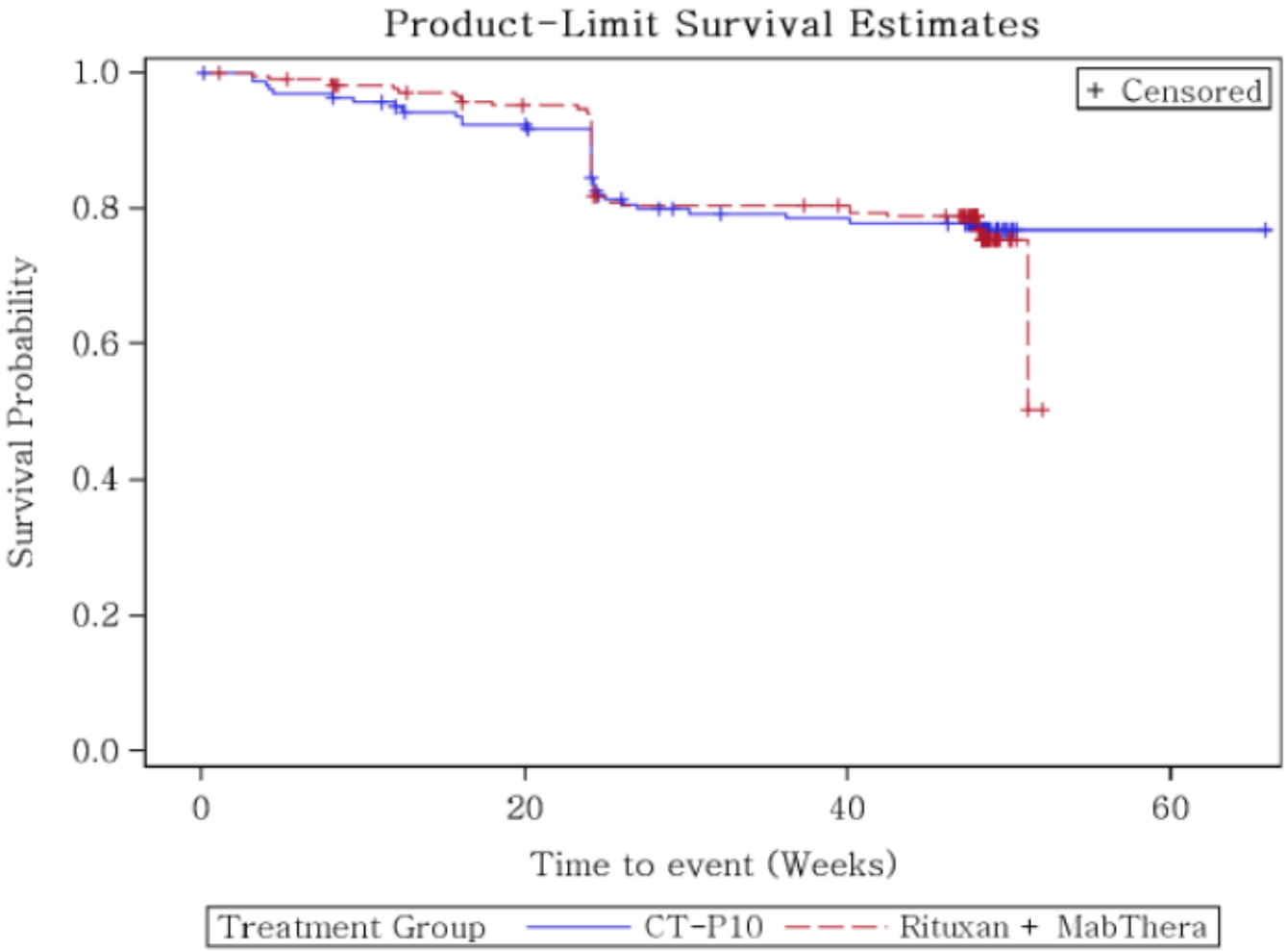


Figure 1: **Time to Event Being First B-cell Value above LLoQ, Retreatment or Discontinuation for Lack of Efficacy Kaplan-Meier Curve in Study CT-P10 1.1: All-randomised/Treated Population**

PD similarity (Study 3.2)

Figure 8: Time to event analysis – all randomised patients in Part 1, part 2



PD similarity

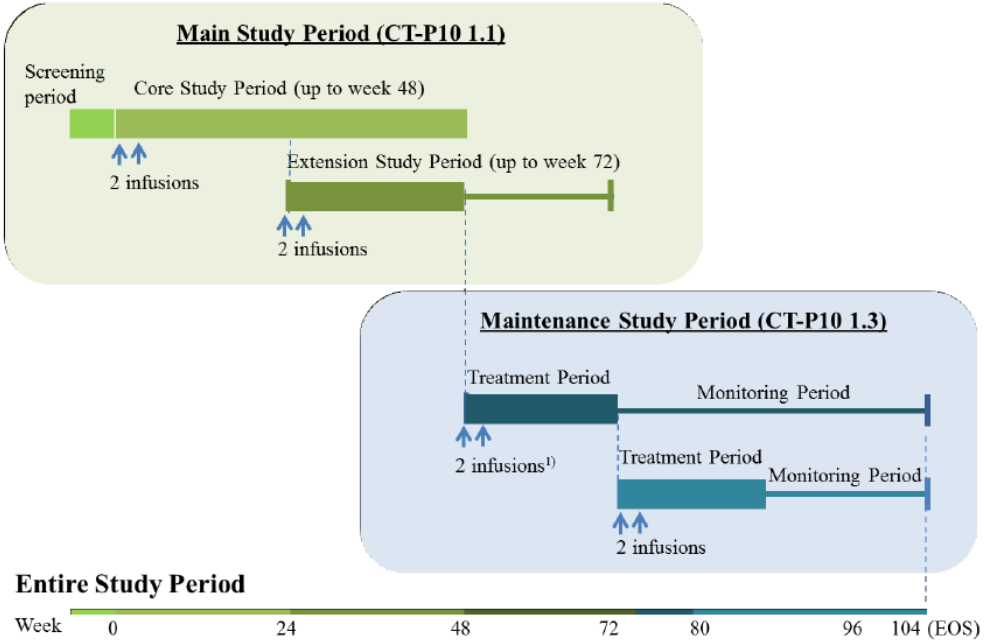
Results from RA studies were initially suggestive of different long-term activity of CT-P10 compared to the reference product.

However, these seem to be a chance finding:

- **No differences from a quality perspective**
- **No statistical evidence of difference**
- **The method used to count B-cells in blood samples lacked sensitivity**
- **No differences in pivotal RA study 3.2**

PD similarity can be assumed

Efficacy similarity (1.1)

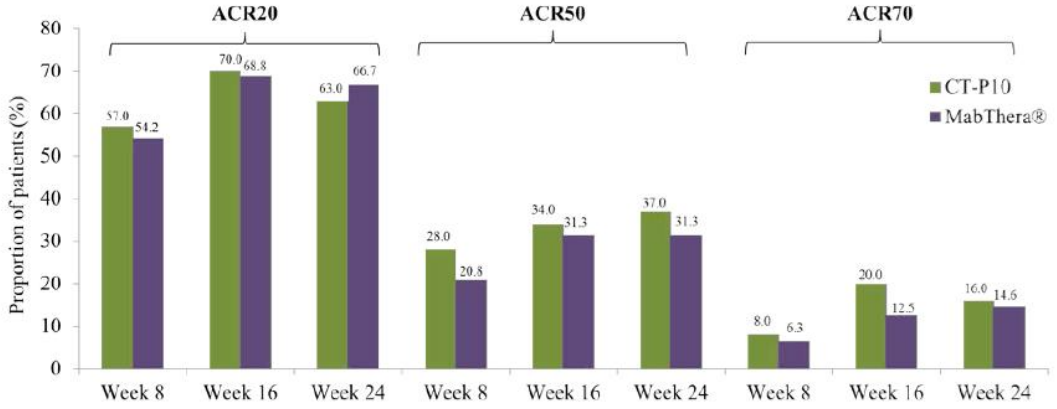


[1)] Patients were assessed for eligibility for CT-P10 infusion during the Monitoring Period. Eligible patients were then permitted to receive CT-P10 in the Treatment Period initiated between the day of enrollment and Week 80 of the Entire Study Period and could receive up to 2 courses of treatment in the maintenance study (up to 4 courses of treatment in the Entire Study Period). Each course consisted of 2 infusions of CT-P10 with a 2 week interval between the first and second infusions.

- **Study CT-P10 1.1**
  A phase 1, randomised, 2-Arm, double blind study to demonstrate PK equivalence in RA

- **Study CT-P10 1.3**
  Open-label, single-arm, multicenter, efficacy, and safety maintenance study of the Phase 1 Study CT-P10 1.1

Efficacy similarity (1.1-2)



ACR: American College of Rheumatology, ACR20: ACR 20% improvement criteria, ACR50: ACR 50% improvement criteria, ACR70: ACR 70% improvement criteria

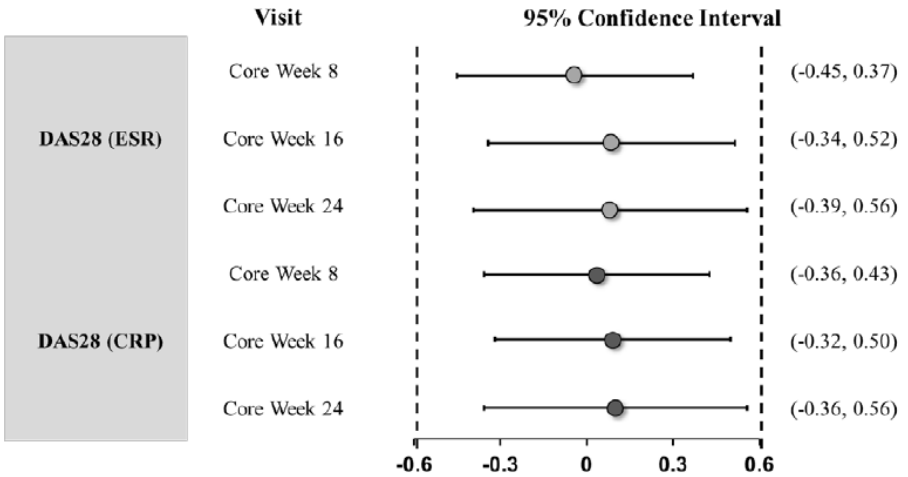


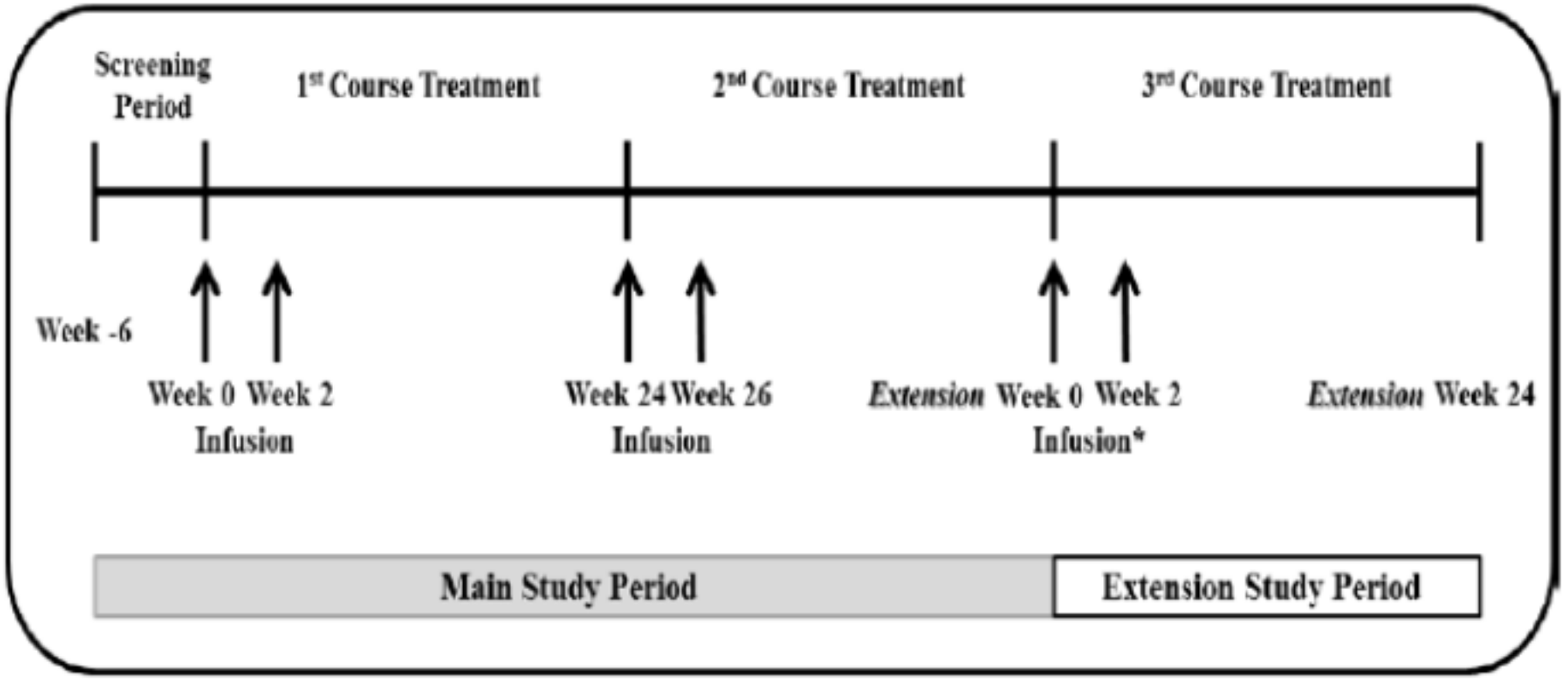
Figure 2.7.3-4: 95% CI Interval for Differences in Mean Change from Baseline of DAS28 in Study CT-P10 1.1: Efficacy Population

CT-P10 1.1

- **No baseline imbalances**
- **Similarity in terms of ACR & DAS 28**

Efficacy similarity (3.2)

Figure 9–1 Overall Study Schematic



- Study CT-P10 3.2

Randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective. 372 patients

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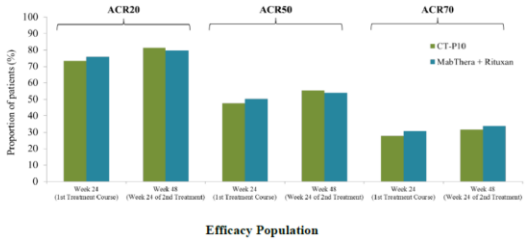
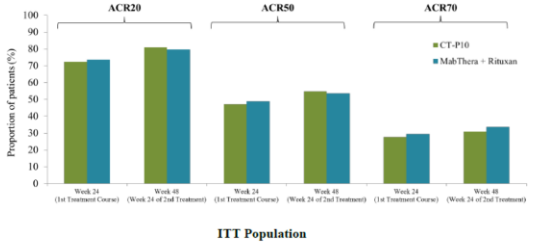
Efficacy similarity

CT-P10 3.2 (long-term data)

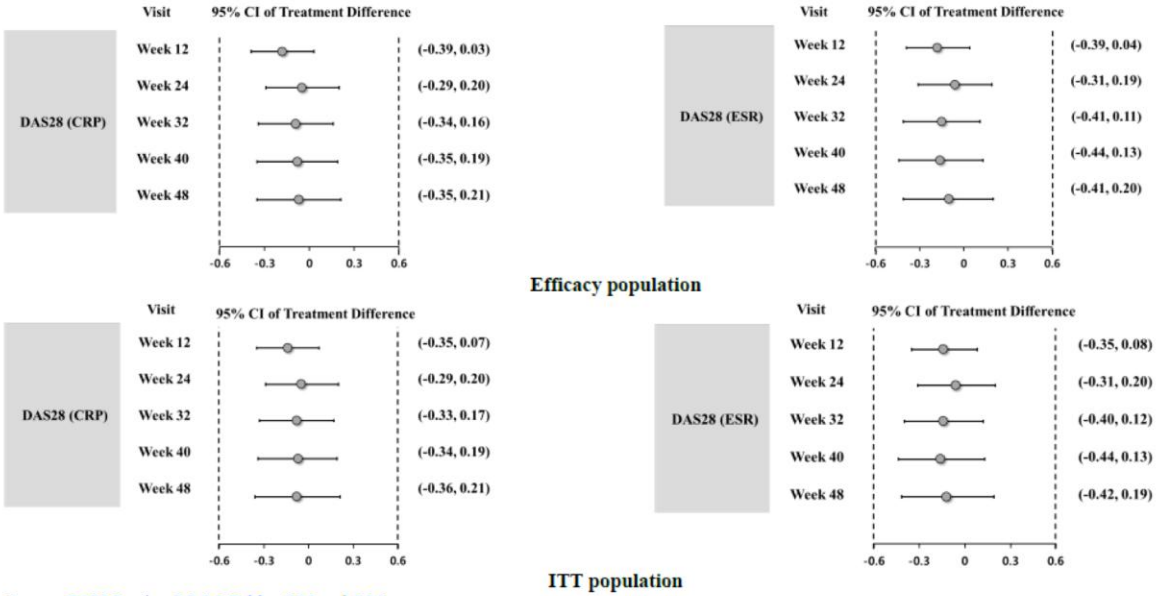
- **Similarity in terms of ACR & DAS 28**





Source: D180 Section 5.3.5.3 Tables 6.12 and 6.13

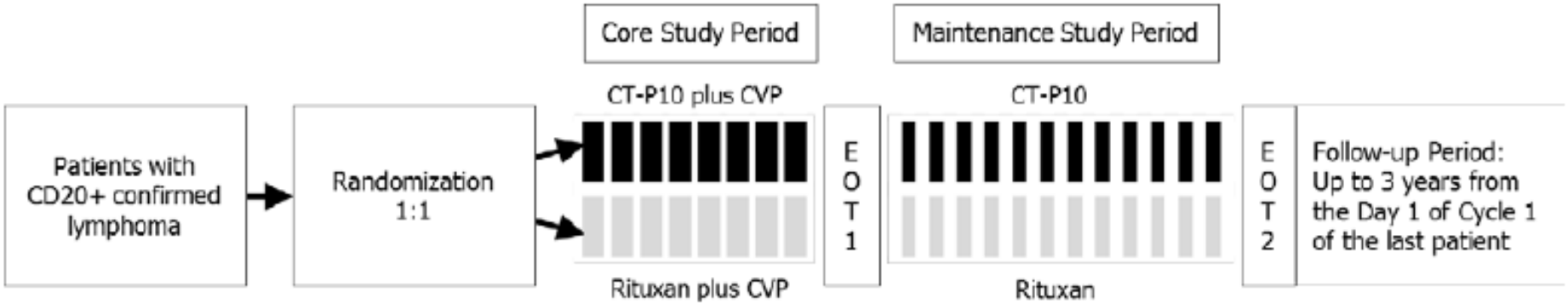
Figure 13: Proportion of Patients Achieving Response according to ACR Criteria (ACR20/50/70) at Week 24 and 48 in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset (Logistic Regression) - Part 2



Source: D180 Section 5.3.5.3 Tables 6.05 and 6.06

Figure 12: ANCOVA Analysis (95% CI for Difference) in DAS28 (CRP, ESR) in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset – Part 2

Efficacy similarity (3.3)



Abbreviations: CD20+, cluster of differentiation 20 positive; CVP, cyclophosphamide, vincristine, and prednisone; EOT1, first end-of-treatment visit; EOT2, second end-of-treatment visit.

A Phase 1/3, Randomized, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 vs CVP

Efficacy similarity

Table 22: Proportion of Patients Achieving ORR (CR + CRu + PR) over Cycle 8 (Week 24) of Core Study Period According to the 1999 IWG Criteria in Study CT-P10 3.3: PP population - Central Review

Number of patients (%)	CT-P10 (N=66)	Rituxan® (N=68)	Difference[1]
ORR (CR + CRu + PR)	64 (97.0)	63 (92.6)	(4.3)
CR	20 (30.3)	15 (22.1)	-
CRu	6 (9.1)	8 (11.8)	-
PR	38 (57.6)	40 (58.8)	-

Sources : CSR Study CT-P10 3.3 Post-text Table 14.2.3.2
[1] Difference was calculated using percentages not the round off values.
ORR: Overall response rate, CR: Complete response, CRu: Unconfirmed complete response, PR: Partial response

ORR difference in study 3.3 (oncology):

4.3% [95%CI -4.14; 13.33] PP

5.7% [95%CI -3.4; 15.4] ITT

Upper bound>7% (Very conservative margin & low sample size)

Safety similarity

	CT-P10 1.1		CT-P10 3.2			Pooled in RA Population (CT-P10 1.1+1.3+3.2)	
	CT-P10 1000 mg	MabThera® 1000 mg	CT-P10 1000 mg	MabThera® 1000 mg	Rituxan® 1000 mg	Total CT-P10 1000 mg	Mabthera® + Rituxan® 1000 mg
	(N=102)	(N=51)	(N=161)	(N=60)	(N=151)	(N=283[1])	(N=262)
Total number of TEAEs	281	142	203	53	161	516	356
Number (%) of patients with ≥ 1 TEAE	73 (71.6)	43 (84.3)	95 (59.0)	33 (55.0)	76 (50.3)	172 (60.8)	152 (58.0)
Related	46 (45.1)	31 (60.8)	49 (30.4)	22 (36.7)	37 (24.5)	97 (34.3)	90 (34.4)
Unrelated	56 (54.9)	30 (58.8)	62 (38.5)	16 (26.7)	55 (36.4)	122 (43.1)	101 (38.5)
Number (%) of patients with ≥ 1 TESAE	14 (13.7)	7 (13.7)	10 (6.2)	0	9 (6.0)	26 (9.2)	16 (6.1)
Related	3 (2.9)	2 (3.9)	0	0	5 (3.3)	3 (1.1)	7 (2.7)
Unrelated	11 (10.8)	5 (9.8)	10 (6.2)	0	5 (3.3)	23 (8.1)	10 (3.8)
Number (%) of patients with ≥ 1 TEAE leading to discontinuation	6 (5.9)	4 (7.8)	3 (1.9)	1 (1.7)	4 (2.6)	9 (3.2)	9 (3.4)
Related	3 (2.9)	3 (5.9)	2 (1.2)	1 (1.7)	4 (2.6)	5 (1.8)	8 (3.1)
Unrelated	3 (2.9)	1 (2.0)	1 (0.6)	0	0	4 (1.4)	1 (0.4)

Benefit-Risk Balance

- For a biosimilar, **the benefit-risk conclusion is based on the totality of evidence collected from the quality, non-clinical, and clinical comparability exercise**. For Truxima the benefit-risk is considered positive based on the submitted data

- **PK data** in both RA and AFL patients **support biosimilarity and the extrapolation** to all other indications

- With regards to the efficacy, it is well established that the mechanism of action and PD aspects are common across autoimmune and across oncology indications of Mabthera. Therefore, and in line with the EMA guidelines on the similar biological medicinal products, the **efficacy results obtained with Truxima, demonstrating equivalence of Truxima and Mabthera in RA and AFL patients can be reasonably extrapolated to the other approved therapeutic indications of Mabthera**

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¡Gracias!

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