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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Blitzima

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/004723/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American college of rheumatology
ACR20	ACR 20% improvement criteria
ACR50	ACR 50% improvement criteria
ACR70	ACR 70% improvement criteria
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AFL	Advanced follicular lymphoma
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the serum concentration-time curve
AUC0-∞	Area under the serum concentration-time curve from the start of first infusion to the infinity covering data from two infusions combined
AUC0-last	Area under the serum concentration-time curve from the start of the first infusion to the last measurable concentration after the second infusion
AUC0-t	Area under the serum concentration-time curve from the start of first infusion to start of the second infusion
AUCt-∞	Area under the serum concentration-time curve from the start of second infusion to infinity
BA	Bioavailability
BE	Bioequivalence
CCP	Cyclic citrullinated protein
CD	Circular dichroism
CDAI	Clinical disease activity index
CDC	Complement-dependent cytotoxicity
CHO	Chinese Hamster Ovary
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	Confidence interval
CIPT	Critical In-process Test
CL	Total body clearance
CLL	Chronic lymphocytic leukaemia
CLT1	CELLTRION Plant I
Cmax	Maximum serum concentration after the second infusion
CLT2	CELLTRION Plant II
Cmax, 1	Maximum serum concentration after the first infusion
Cmin	Minimum serum concentration immediately before the second course
CPP	Critical Process Parameter
CR	Complete response
CQA	Critical Quality Attribute
CRP	C-reactive protein
CRu	Unconfirmed complete response
CSR	Clinical safety report
Ctrough	Concentration before the 2nd infusion
CV	Coefficient of variation
CVP	Cyclophosphamide, vincristine, prednisolone
C1q	A subunit of the C1q enzyme complex
DAS28	Disease activity score using 28 joint counts
DLBCL	Diffuse large B-cell lymphomas
DMARD	Disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ECL	Electrochemiluminescence
FcγRI	Fc gamma receptor R1 (CD64)
ESR	Erythrocyte sedimentation rate

FcγRIIIa-V	Fc gamma receptor 3a (CD16a) V type receptor
EULAR	European league against rheumatism
FcRn	neonatal Fc receptor
GCP	Good clinical practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GPA	Granulomatosis with polyangiitis
HACA	Human anti-chimeric antibodies
HAQ	Health assessment questionnaire disability index
HBV	Hepatitis B virus
HCP	Host Cell Protein
HMW	Higher Molecular Weight
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	Immunoglobulin
IPC	In-process control
IRR	Infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
LLN	Lower limit of normal
LLoQ	Lower limit of quantification
LMW	Low Molecular Weight
LOCF	Last observation carried forward
LTBFL	Low-tumour-burden follicular lymphoma
MCB	Master cell bank
MoA	Mechanism of action
MPA	Microscopic polyangiitis
MTX	Methotrexate
NA	Not available
NAb	Neutralising antibody
NHL	Non–Hodgkin's lymphoma
NANA	N-Acetylneuraminic acid
NSAID	Non-steroid anti-inflammatory drugs
OOS	Out of Specification
ORR	Overall response rate
PBMCs	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PPD	Pharmaceutical Product Development, LLC
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
PY	Patient-year
QbD	Quality by Design
RA	Rheumatoid arthritis
QTPP	Quality Target Product Profile
RF	Rheumatoid factor
RH	Relative humidity
RMP	Risk management plan
SAE	Serious adverse events
SD	Standard deviation
SDAI	Simplified disease activity index
SF-36	Short form (36) health survey
SJS	Stevens–Johnson syndrome
SmPC	Summary of product characteristics
SOC	System organ class
T1/2	Terminal elimination half-life
TB	Tuberculosis

TEAE	Treatment emergent adverse event
TEN	Toxic epidermal necrolysis
TESAE	Treatment emergent serious adverse event
Tmax	Time to maximum serum concentration after the second infusion
Tmax, 1	Time to maximum serum concentration after the first infusion
TNF	Tumour necrosis factor
US	United States
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 6 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Blitzima, through the centralised procedure. As this application concerns active substance already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 15 December 2016.

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a duplicate of Truxima authorised on 17 February 2017.

The applicant applied for the following indications:

Non-Hodgkin's lymphoma (NHL)

Blitzima is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Blitzima maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Blitzima monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.

Blitzima is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Blitzima in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Blitzima or patients refractory to previous Blitzima plus chemotherapy.

Granulomatosis with polyangiitis and microscopic polyangiitis

Blitzima, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: MabThera, 500 mg, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1998-06-02
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/067/002

Medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: MabThera, 500 mg, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1998-06-02
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/067/002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: MabThera, 500 mg, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1998-06-02
- Marketing authorisation granted by:

- Community

- Community Marketing authorisation number: EU/1/98/067/002

Scientific Advice

Blitzima has not received any Scientific Advice from the CHMP, however scientific Advice was given for Truxima on 18 March 2010 (EMEA/H/SA/1532/1/2010/II); 21 October 2010 (EMEA/H/SA/1532/2/2010/II); 17 March 2011 (EMEA/H/SA/1532/2/FU/1/2011/III);19 May 2011 (EMEA/H/SA/1532/2/FU/1/2011/III); 17 January 2013 (EMEA/H/SA/1532/2/FU/2/2012/II); 20 February 2014 (EMEA/H/SA/1532/2/FU/3/2014/II). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:

Biosimilar rituximab (Truxima) was granted a positive opinion from the CHMP on 15 December 2016. The European Commission granted a marketing authorisation valid throughout the European Union for Truxima on 17 February 2017. This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a duplicate of Truxima.

Biosimilar rituximab has been authorised in South Korea in November 2016.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Sol Ruiz

- The application was received by the EMA on 06 March 2017
- The procedure started on 20 March 2017
- The Rapporteurs circulated the Joint Assessment Report addressing similarity with authorised orphan medicinal products on 27 April.
- The CHMP and PRAC Rapporteur's Assessment Report was circulated to all CHMP members on 04 May 2017.
- During the meeting on 18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Blitzima on 18 May 2017.

2. Scientific discussion

Introduction

Rituximab was first authorised in the European Union on 2 June 1998 under the name of MabThera. It is also marketed under the name Rituxan in the United States (US). It is currently approved for the following indications:

Non-Hodgkin's lymphoma (NHL)

- treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
- maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy.
- monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.
- treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

- in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia.

Rheumatoid arthritis
in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis
in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).
The conditions covered by the above indications have been extensively analysed through the respective approval procedures of Mabthera (see Mabthera European assessment report – EPAR)

Rituximab is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. CD20 is located on pre-B and mature B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal cells. CD20 is also expressed on >95% of all B-cells in non-Hodgkin lymphoma. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.CD20 regulates an early step in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. After binding to the CD20 antigen on the cell surface, rituximab exerts its therapeutic effect by promoting B-cell lysis.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

The therapeutic benefit of the destruction of malignant B-cells in the oncological indications of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia CLL results in control of tumour growth and translates in extension of survival.

B-cells also play several important roles in the pathogenesis of rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). They produce auto-antibodies such as Rheumatoid Factor (RF), anti-cyclic citrullinated protein (anti-CCP) antibody in RA or anti-neutrophil cytoplasmic antibody (ANCA) in MPA and CPA. In the synovium, RF immune complexes may mediate complement activation and the propagation of the inflammatory cascade. B-cells present in the RA synovial membrane may secrete a range of pro-inflammatory cytokines, some of which are components in the process leading to joint inflammation and damage, or to induce leukocyte infiltration. B-cells can function as antigen-presenting cells and immune-regulatory cells, leading to T-cell activation. They can also stimulate osteoclasts and synovial fibroblasts and lead to bone erosions and joint tissue remodelling.

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month time point. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

Mabthera is available as 100mg and 500 mg strengths as concentration for solution for iv infusion and as 1400 mg and 1600 mg as solution for sc injection.

About the product

Blitzima (also referred to as CT-P10) contains the active substance rituximab and has been developed as a similar biological medicinal product to the reference medicinal product MabThera.

The formulation development process for Blitzima has been designed to replicate MabThera and both products are identical with respect to the pharmaceutical form and composition for the iv route of administration and the strength of 500mg.

The proposed therapeutic indications and posology for CT-P10 are identical to those for MabThera, to which similarity is claimed.

Type of Application and aspects on development

This Marketing Authorisation Application (MAA) is an abridged application for a similar biological medicinal product CT-P10 under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC. Similarity

for CT-P10 is claimed to the reference medicinal product MabThera for intravenous (IV) use as the reference medicinal product, which has been approved in the European Union (EU) in February 1998 (EMEA/H/C/000165).

To demonstrate that the similar biological and reference products already authorised in the community have similar profiles in terms of quality, safety and efficacy an extensive comparability exercise is required. The clinical development programme of CT-P10 has specifically considered the EU guidelines for similar biological medicinal products and bioequivalence:

Table 1: EU Guidelines Considered for Blitzima Clinical Development Programme

Guideline	Document Reference
Guideline on Similar Biological Medicinal Products. 2015	CHMP/437/04 Rev.01
Draft Guideline on Similar Biological Medicinal Products.	CHMP/437/04 Rev. 01
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues. 2014	CHMP/BWP/247713/2012
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. EMEA, 2015	EMEA/CHMP/BMWP/42832/2005 Rev. 1
Guideline on similar biological medicinal products containing monoclonal antibodies	EMA/CHMP/BMWP/403543/2010
Guideline on the investigation of bioequivalence. EMEA, 2010	CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, 2007	EMEA/CHMP/BMWP/14327/2006
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. EMEA, 2007	CHMP/EWP/89249/2004

Although no specific Sicentific Advice has been applied for Blitzima, during the development of Truxima, of which Blitzima is a duplicate, the applicant sought scientific and procedural advice at the European Medicines Agency (EMA). The scientific advice procedures covered questions on the pharmaceutical quality, the nonclinical and clinical programme.

Blitzima will be available as 500 mg concentration for solution for infusion.

2.1. Quality aspects

2.1.1. Introduction

Blitzima quality package is exactly the same as that submitted for the MAA of Truxima, thus the final assessment report adopted for Truxima is shown below:

The active substance CT-P10 (rituximab) is a chimeric monoclonal IgG1 antibody that binds to CD20, which is primarily found on the surface of malignant and normal B cells.

The finished product is presented as sterile solution for injection containing 500 mg of CT-P10 (rituximab) as active substance.

Other ingredients are sodium chloride, tri-sodium citrate dihydrate, polysorbate 80 and water for injections.

The product is available in clear Type I glass vials with a butyl rubber stopper and a flip-off seal.

2.1.2. Active Substance

General information

The active substance, CT-P10 (rituximab), is a chimeric monoclonal IgG1 antibody subclass. Like other IgG subclasses, CT-P10 is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues and each light chain consists of 213 amino acids with 5 cysteine residues.

CT-P10 binds to the CD20 antigen found on the surface of malignant and normal B cells. By binding to CD20 antigen, the main mechanisms of CT-P10 are complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis.

Manufacture, process controls and characterisation

The CT-P10 active substance is manufactured, packaged, stability and quality-control tested in accordance with good manufacturing practice (GMP).

Description of manufacturing process and process controls

The CT-P10 active substance manufacturing process has been adequately described. Main steps are fermentation, recovery, purification and filling. The ranges of critical process parameters and the routine in-process controls, along with acceptance criteria, are described for each step. The active substance manufacturing process is considered acceptable.

The production process follows a standard procedure for monoclonal antibodies production; starting from the thawing of a vial of the WCB followed by several cell expansion steps before final bioreactor production. CT-P10 is purified through a series of chromatographic (affinity and ion-exchange) and filtration steps, including 4 dedicated viral inactivation steps (2 chromatography steps, low-pH treatment and nanofiltration). Each step of the purification process has been adequately described, including descriptions of the different buffers used, column regeneration and storage conditions. Process hold steps are detailed and appropriate data to support product intermediate hold times has been provided. The critical process parameters for each process step are justified and appropriate in-process controls, with justified acceptance limits, are specified. In-process control tests are sufficient to ensure the microbial/viral safety of the product, and consistent quality.

A batch of CT-P10 active substance is manufactured from a single 15,000 L production bioreactor.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

No raw materials of human origin are used during active substance manufacture. Only one animal derived material is used in the manufacturing process of active substance. Acceptable documents have been provided for raw materials including animal derived material of biological origin used in the establishment of cell substrate.

A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

Information on the development genetics including origin of the gene based on the published amino acid sequence and DNA sequence of rituximab using polymerase cycling assembly, description of the gene construction (components, position, origin, function and reference) and rationale behind the genes construct have been provided. In addition, the origin of the CHO cell line used to be transfected has been also described. The applicant provided the details on the transfection process. In the context of viral safety the applicant has demonstrated that testing of the MCB and WCB is sufficient for product quality.

The production of the MCB and WCBs is well described. In general terms, the cell banks were extensively characterized to confirm their identity, freedom from adventitious agents, and also genetically characterized in relation to the integrated recombinant plasmid. All tests were done according to current guidelines, and all the results obtained ensure that both banks meet all required specifications.

The applicant states that the new WCB will be generated by a qualified manufacturer that will be selected in the future employing the same or equivalent quality of raw materials, method, controls and tests used to generate the 1st WCB. In addition, the newly generated WCB will be appropriately qualified by characterisation and testing in accordance with ICH guidelines. Finally, the results will be submitted prior to introduction of the new WCB for production, as part of a post-approval variation to the marketing authorisation.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the CT-P10 active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the drug substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Sufficient information has been presented to understand the approach followed to establish the manufacturing control strategy. Taking account of the Quality Target Product Profile (QTPP) of CT-P10 finished product, Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs) and Critical In Process Controls (CIPTs) relating to CT-P10 active substance have been defined.

CQAs were first established using a combination of risk assessment, data from early development, process characterization studies and commercial scale production. The in-process controls (CPPs and CIPTs) were selected and form part of the control strategy along with the release specifications.

The types of controls and overall control strategy are appropriate for the control of a monoclonal antibody. The control ranges for all the controls (critical and non-critical) have been provided in the application.

Process validation

The CT-P10 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces CT-P10 active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Several other aspects have also been validated or evaluated, including impurity clearance, resins life time and membranes lifetime. Filter validation and in-process hold studies were also carried out.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. During product development, changes to the manufacturing process have been implemented to improve process and product consistency, these have been well documented in the submission. Appropriate product comparability studies have been carried out to demonstrate the process changes have not impacted on key product quality attributes.

Characterisation

The CT-P10 active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG-type antibody. The primary, secondary, and higher-order structure, post-translational modifications, glycosylation, charge variants, purity/impurities, quantity and biological properties were elucidated using orthogonal analytical techniques.

To assess the biological activity of CT-P10, a number of different assays, chosen to represent the putative mechanisms of action of rituximab, have been used for characterisation purposes. The applicant demonstrated relevant and consistent biological activity of CT-P10 for all batches of active substance and finished product tested. In addition, the applicant performed a series of studies of the biological activity of CT-P10 finished product relative to the reference product (MabThera and Rituxan) as part of the similarity/comparability assessment. Overall, the techniques applied for characterisation on CT-P10 are considered adequate and provide a thorough characterisation of the molecule.

Specification

The proposed active substance specification includes tests for Colour (Ph. Eur.), Clarity (Ph. Eur.), Visible Particles (Ph. Eur.), pH (Ph. Eur.), Identity, Oligosaccharide Profile, Purity, Residual HCP, Residual Host Cell DNA, Residual rProtein A, Protein Concentration, Potency, Endotoxin (Ph. Eur.), Bioburden (Ph. Eur.).

The proposed release specification covers the relevant characteristics of monoclonal antibodies. Acceptance limits are well justified and reflect manufacturing experience. The specification is considered appropriate to ensure the quality of the active substance.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data of the active substance manufactured by the development and commercial processes were provided. The results are within the specifications and confirm consistency of the manufacturing process, with some minor variations between manufacturing processes already explained in the comparability studies.

Reference materials

The history of reference standards used during development was presented. A working reference standard will be established post-approval after qualification against the primary reference standard.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container, when protected from light.

Long-term, intermediate and accelerated stability studies have been conducted on representative batches of CT-P10 active substance. The parameters tested on stability were a subset of the release specification selected for stability indicating properties. The results of the photostability studies suggest the active substance is photo-sensitive and should be stored protected from light.

2.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as sterile solution for injection containing 500 mg of CT-P10 as active substance.

Other ingredients are sodium chloride, tri-sodium citrate dihydrate, polysorbate 80 and water for injections.

The primary packaging is clear Type I glass vials with a butyl rubber stopper and a flip-off seal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Finished product development

The development strategy of CT-P10 was focused on developing a similar biological medicinal product comparable to the reference medicinal product, MabThera. To this end the finished product formulation used in non-clinical and clinical development and which will be used for commercial supply is identical to MabThera (pH 6.5, 25 mM sodium citrate, 154 mM NaCl, 0.07 % polysorbate 80). Therefore, limited qualitative and quantitative formulation studies have been performed, the purpose of which was to demonstrate the formulation used was adequately robust in terms of product stability and quality and comparable with MabThera.

Overall, the chosen formulation showed good stability and similar degradation rates compared to MabThera.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

CT-P10 finished product does not include an overage. A 3% overfill has been justified with a volume of 51.5 mL to ensure the required volume for administration can be removed from the vial.

Manufacturing process development

The development of the CT-P10 finished product manufacturing process has been described over pilot, clinical and proposed commercial scales. Acceptable comparability between these development batches and the commercial batches has been demonstrated.

Manufacture of the product and process controls

CT-P10 solution for injection is manufactured in accordance with good manufacturing practice (GMP).

The manufacturing process is standard and well described. It comprises the following steps:

1. Preparation of formulation buffer,
2. Formulation of active substance,
3. Sterile filtration,
4. Aseptic filling,

5. Capping, inspection and storage.

An appropriate control strategy is in place and has been described in detail with process parameters as well as in-process tests/in-process monitoring. A number of questions were raised to clarify specific points. The criticality of quality attributes for the CT-P10 finished product manufacturing process has been determined as for the active substance using risk assessment and development data as well as commercial scale production data. The manufacturing process has been validated. The validation studies confirmed the robustness and consistency of the manufacturing process for CT-P10 finished product. Hold times have been validated and shipping validation has been completed. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The proposed finished product specification includes tests for Colour (Ph. Eur.), Clarity (Ph. Eur.), Visible Particles (Ph. Eur.), pH (Ph. Eur.), Extractable Volume (Ph. Eur.), Osmolality (Ph. Eur.), Uniformity of Dosage Units (Ph. Eur.), Sub-visible particles (Ph. Eur.), Endotoxin (Ph. Eur.), Sterility (Ph. Eur.), Identity, Purity, Protein Concentration and Potency.

The end-of-shelf-life specifications are the same as those applied at release.

The specifications were established based process capability and the analyses of multiple batches of CT-P10 finished product. The specification is considered appropriate to ensure the quality of the finished product.

Analytical methods

The majority of methods are used to control both the active substance and finished product except for Extractable Volume (Ph. Eur.), Osmolality (Ph. Eur.), Uniformity of Dosage Units (Ph. Eur.), Sub-visible particles (Ph. Eur.), Sterility (Ph. Eur.).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data of multiple batches were provided. The results are within the specifications and confirm consistency of the manufacturing process. The quality of CT-P10 active substance and finished product is similar without additional impurities detected in the CT-P10 finished product.

Reference materials

The reference standard used for control of CT-P10 active substance is also used for the control of CT-P10 finished product.

Stability of the product

Based on available stability data, the proposed shelf-life of CT-P10 finished product of 3 years when stored at 2°C - 8°C with the container kept in the outer carton in order to protect from light, is acceptable.

Furthermore, the prepared infusion solution of rituximab following dilution with 0.9% NaCl has been shown to be physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature (not more than 30 °C).

The stability data included long-term and accelerated stability studies, conducted in accordance with the relevant ICH guidelines. The parameters tested on stability were as per the release specification. A confirmatory photostability study following the ICH guideline Q1B was also performed. The applicant performed a forced degradation study in order to characterise and understand the processes and pathways associated with CT-P10 degradation. An in-use stability study of CT-P10 following dilution in 250 ml of 0.9% w/v sodium chloride (NaCl) solution was performed. The results confirmed that the diluted product was physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature (not more than 30 °C).

Adventitious agents

Raw materials

No raw materials of human origin are used during CT-P10 manufacture. One component of the cell culture medium is the only material used during the manufacture of CT-P10 active substance. An overview of the viral safety of raw materials of biological origin used during cell line development and during CT-P10 manufacture was presented.

Cell Banking System

MCB, WCB, and EPCB were tested for the presence of endogenous and adventitious viruses using validated methods.

Viral Testing of Unprocessed Bulk

Adventitious viruses were not detected in any of the harvest lots tested. Retrovirus-like particles for unprocessed bulk were not detected by TEM above the limit of detection of the assay.

Virus Clearance Study

The Virus Clearance Study was considered adequate. The raw data of this study was requested during the procedure and have been provided.

Biosimilarity

CT-P10 has been developed as a similar biological medicinal product to the EU reference product MabThera (rituximab) for intravenous (IV) use, which is also marketed under the name Rituxan in the US. CT-P10 finished product was designed to be highly similar to its reference medicinal product, MabThera. CT-P10 and MabThera are identical with respect to pharmaceutical form, concentration and composition, and route of administration. CT-P10 solution for injection contains 500 mg rituximab per vial which is identical to the content of both MabThera and Rituxan.

A step-wise approach has been taken with respect to the demonstration of similarity of CT-P10 to MabThera, starting with a comprehensive physicochemical and biological characterization of CT-P10 relative to its reference product. This similarity exercise was undertaken, not only to demonstrate the similarity of CT-P10 to MabThera, but also to demonstrate the similarity of Rituxan to MabThera, in order to support the global registration of CT-P10 in the future.

The applicant has performed a large number and wide range of orthogonal, highly sensitive test methods to provide a demonstration of similarity. The similarity studies included an extensive comparative analysis of primary, secondary and tertiary structure, glycan profiles and of post translational modifications. In addition, biological assays were included to evaluate similarity in all biological activities associated with known and

putative functions and therapeutic effects. The analytical methods and biological assays used in similarity studies have been suitably validated or qualified to provide a high level of assurance that the methods could detect any slight differences and are scientifically sound, fit for purpose, reliable and reproducible.

Representative batches of CT-P10 finished product, MabThera and Rituxan were analysed to assess the similarity between CT-P10, MabThera and Rituxan. All MabThera batches were sourced from the EU while all Rituxan batches were sourced from the US. The batches of CT-P10, MabThera, and Rituxan were chosen to reflect a range of expiration dates and product ages. All batches were within the shelf life at the time of testing and were stored and handled as recommended in the labelling.

It was considered that a sufficient number of batches from CT-P10, MabThera and Rituxan had been chosen and the tests panels were extensive. A justification for the use of only CT-P10 finished product batches based on feedback from CHMP Scientific Advice was accepted. In addition, any deviation from the advice given by the EU authorities was adequately justified.

The results of the 3-way comparability study presented by the applicant show that CT-P10 and MabThera/Rituxan can be considered similar in terms of structure and biological activity. Identical primary structure was shown using methods such as amino acid analysis, molar absorptivity, N-terminal sequencing, C-terminal sequencing, peptide mapping, and determination of intact mass. Highly similar secondary and higher order structure was shown using methods such as Fourier Transform Infra-Red spectroscopy (FTIR), Circular Dichroism (CD), Differential Scanning Calorimetry (DSC). Similar post-translational modifications included deamidation, oxidation and C-terminal lysine variants, similar number and distribution of charged variants and highly similar glycosylation profiles, highly similar monosaccharide (Fucose, N-acetyglucosamine, Galactose and Mannose) sugar contents and sialic acid (N-acetylneuraminic acid (NANA)) contents and similar levels of residual process-related impurities (such as host cell protein, Host Cell DNA and rProtein A) were shown.

Some slight differences were observed which were shown not to have any impact on biological activity, safety or PK, and therefore they are considered acceptable.

Highly similar binding affinity to CD20 (the primary mechanism of action of rituximab) and highly similar biological activities in assays representative of the known and putative mechanisms of action of Rituximab, namely, CDC, ADCC, apoptosis, C1q binding affinity, Fcγ receptors (FcγRIIIa-V, FcγRIIIa-F, FcγRIIIb, FcγRIIa, FcγRIIb and FcγRI) binding affinity and FcRn binding affinity was shown. A similar correlation between glycosylation and Fc function of CT-P10 and MabThera/Rituxan was also shown.

Comparative forced degradation studies of CT-P10 and MabThera/Rituxan were performed. The degradation profiles of CT-P10 and MabThera/Rituxan were shown to be comparable.

Comparative stability testing was performed. The results of stability testing did not reveal any differences that could have implications for the safety or efficacy of CT-P10.

Before concluding on the biosimilarity of the three products the CHMP requested additional information and/or clarification from the applicant.

The applicant provided more information about the age/shelf-life of the batches used in the biosimilarity assessment and it demonstrated that the age of the batches has no effect on the quality profile of CT-P10 compared to MabThera and Rituxan.

The applicant reconfirmed that the number, distribution and molecular variants of IEC-HPLC peak fractions were conserved and the biological activities of the peak fractions were similar among the fully characterised CT-P10, MabThera and Rituxan lots, consistent with the results previously reported in the initial dossier.

The applicant performed an evaluation of functional assays, potency and binding affinity related to putative mechanisms of action (apoptosis, CDC and ADCP) using different samples obtained from NHL and CLL patients to support the extrapolation of the clinical results obtained from the rheumatoid arthritis indication to other indications of MabThera authorised in the EU.

The applicant demonstrated similar biological activities for CT-P10 and MabThera in assays representative of the known and putative mechanisms of action of Rituximab, regardless of the source of cells. These data suggest that CT-P10 and MabThera will have highly similar therapeutic effects across all indications for which MabThera is approved in the EU.

In conclusion, the full set of biosimilarity data presented is considered appropriate. The biosimilarity of CT-P10 to the EU reference product (MabThera) has been demonstrated at the quality level. Any minor differences observed have been adequately justified. In addition, based on analytical bridging data, the US comparator product Rituxan is considered representative of the EU reference product MabThera.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

CT-P10 has been developed as a biosimilar to the EU reference product MabThera. Overall, similarity between CT-P10 and the EU reference product MabThera is considered demonstrated at the quality level. Any minor differences observed have been adequately justified. In addition, based on analytical bridging data, the US comparator product Rituxan is considered representative of the EU reference product MabThera.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of CT-P10 is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.1.6. Recommendation(s) for future quality development

n/a

2.2. Non-clinical aspects

2.2.1. Introduction

Blitzima non-clinical package is exactly the same as that submitted for the MAA of Truxima, thus the final assessment report adopted for Truxima is shown below:

The primary pharmacodynamic of CT-P10 was evaluated in comparison with the reference rituximab products, Mabthera / Rituxan.

The primary pharmacodynamic of rituximab (CT-P10) was evaluated in comparison with the reference products, Mabthera (Rituximab) and Rituxan (Rituximab).

A repeat-dose toxicity study comparing CT-P10 and MabThera was performed in both sexes cynomolgus monkeys at dose of 20 mg/kg (Study No. ZIP0003). The toxicokinetic (TK) analysis was included as part of the repeat-dose toxicity study which was performed in compliance with OECD GLP according to EU requirements.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro comparative binding affinity of CT-P10, MabThera and Rituxan to CD20 by CELISA

The binding activity of CT-P10 was investigated in cell line expressing CD20. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 2) at the same experimental conditions.

Table 2: Summarized analysis of cell-based CD-20 binding affinities

Product	CT-P10	MabThera	Rituxan
Mean	97	96	96
SD	5.8	6.2	7.0
Quality range (QR) of MabThera	77.4-114.5		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Apoptosis of CT-P10, MabThera and Rituxan using CD20-expressing cell line

Apoptosis induction in the cell line expressing CD20 was assessed by FACS (annexin V-FITC/PI staining). The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 3) at the same experimental conditions.

Table 3: Summarized analysis of the relative apoptotic activity

Product	CT-P10	MabThera	Rituxan
Mean	103	101	99
SD	3.1	5.1	5.0
Quality range (QR) of MabThera	86.1-116.8		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcRn using SPR

FcRn binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 4) at the same experimental conditions.

Table 4: Summarized analysis of the FcRn binding affinity

Product	**CT-P10**	**MabThera**	**Rituxan**
Mean	101	100	100
SD	2.4	2.3	2.2
Quality range (QR) of MabThera	92.1-106.9		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRI using SPR

FcγRI binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 5) at the same experimental conditions.

Table 5: Summarized analysis of the FcγRI binding affinity

Product	**CT-P10**	**MabThera**	**Rituxan**
Mean	100	101	100
SD	3.0	3.2	2.6
Quality range (QR) of MabThera	91.2-110.4		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRIIa using SPR

FcγRIIa binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 6) at the same experimental conditions.

Table 6: Summarized analysis of the FcγRIIa binding affinity

Product	CT-P10	MabThera	Rituxan
Mean	**99**	**100**	**100**
SD	3.3	3.0	3.3
Quality range (QR) of MabThera	91.2-109.5		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRIIb using SPR

FcγRIIb binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 7) at the same experimental conditions.

Table 7: Summarized analysis of the FcγRIIb binding affinity

Product	CT-P10	MabThera	Rituxan
Mean	98	97	94
SD	7.1	5.6	6.7
Quality range (QR) of MabThera	80.2-113.8		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRIIIa (F type) using SPR

FcγRIIIa (F type) binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 8) at the same experimental conditions.

Table 8: Summarized analysis of the FcγRIIIa (F type) binding affinity

Product	CT-P10	MabThera	Rituxan
Mean	100	108	105
SD	2.5	8.6	8.9
Quality range (QR) of MabThera	82.1-134.0		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRIIIa (V type) using SPR

FcγRIIIa (V type) binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 9) at the same experimental conditions.

Table 9: Summarized analysis of the FcγRIIIa (V type) binding affinity

Product	CT-P10	MabThera	Rituxan
Mean	100	104	103
SD	3.3	6.6	6.9

Quality range (QR) of MabThera	84.3-123.8		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to FcγRIIIb using SPR

FcγRIIIb binding affinity was evaluated and K_D values obtained. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 10) at the same experimental conditions.

Table 10: Summarized analysis of the FcγRIIIb binding affinity

Product	CT-P10	MabThera	Rituxan
Mean	**102**	**105**	**101**
SD	7.7	8.5	8.8
Quality range (QR) of MabThera	79.5-130.5		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

ADCC activity of CT-P10 and the reference products

ADCC activity was evaluated using CD20-expressing cell lines and PBMCs from healthy donor as effector cells. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 11) at the same experimental conditions.

Table 11: Summarized analysis of the ADCC activity

Product	**CT-P10**	**MabThera**	**Rituxan**
Mean	97	97	98
SD	6.0	4.3	4.0
Quality range (QR) of MabThera	83.8-109.4		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Binding affinity of CT-P10 and the reference products to C1q by ELISA

Binding affinity to C1q was evaluated using ELISA. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 12) at the same experimental conditions.

Table 12: Summarized analysis of the binding affinity to C1q

Product	CT-P10	MabThera	Rituxan
Mean	104	104	105
SD	7.8	6.1	4.8
Quality range (QR) of MabThera	85.1-122.0		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

CDC activity of CT-P10 and the reference products

CDC effect was evaluated on CD20-expressing cells. The results of CT-P10 were compared with those obtained with MabThera and Rituxan (Table 13) at the same experimental conditions.

Table 13: Summarized analysis of the CDC activity

Product	CT-P10	MabThera	Rituxan
Mean	100	100	99
SD	3.8	5.3	3.3
Quality range (QR) of MabThera (	84.5-116.2		
% batches within QR	100	NA	100

The results obtained for CT-P10 fell within the established QR of MabThera.

Cross reactivity assessment of CT-P10 and MabThera in human tissues (GLP compliant)

A cross-reactivity study was carried out with the aim of compare the reactivity of CT-P10 and MabThera in human tissues. The samples were obtained from three unrelated donors and tonsil tissue was selected as positive control. The results showed a very similar staining profile for both products in tissues expressing CD20 (tonsil, lymph node, thymus and spleen).

Unspecific binding in white matter and peripheral nerve was recorded. Nuclear staining was considered non-relevant due to nuclei were not accessible in in vivo studies.

In vivo pharmacodynamics effects of CT-P10 and MabThera in cynomolgus monkeys (GLP compliant)

The in vivo pharmacological activity of CT-P10 was evaluated in cynomolgus monkeys. Animals received intravenously CT-P10 or MabThera during 8 weeks on a weekly basis (20 mg/Kg/week). A similar effect in terms of B-cells depletion was observed in both treatments. CT-P10 induced changes in the mesenteric lymph nodes

and spleens of males and females. In the case of animals treated with MabThera, similar changes were observed in mesenteric lymph nodes, although only in the spleens of males.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed, which is acceptable for a biosimilar product.

Safety pharmacology programme

Safety pharmacology related parameters were incorporated in the repeated dose toxicology study. In this study, no treatment related findings (electrocardiography, body temperature) were reported.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were performed which is acceptable for a biosimilar product.

2.2.3. Pharmacokinetics

8-week GLP Repeat iv Dose Toxicokinetic Study in Cynomolgus Monkey using CT-P10 (rituximab) and MabThera (rituximab)

This study compared the toxicokinetics of CT-P10 and Mabthera to establish that the products had similar TK parameters (Cmax, AUC0-168h, C168, Tmax). Blood samples were taken on Day 1 and Day 22 from 3 males and 3 female cynomolgus monkeys to CT-P10 or MabThera after weekly IV administration (bolus) at 20 mg/kg/week. One male in CT-P10 group and 1 male and 2 females in MabThera group were excluded from the PK assessment due to the detection of anti-drug antibody production on Day 22. Among them, 1 male and 1 female in Mabthera group were prematurely sacrificed (on Days 36 and 29 respectively) due to adverse clinical signs.

Table 14: Analysis of Serum AUC0-168h and Cmax of CT-P10 and MabThera in Cynomolgus Monkeys following Intravenous Doses at 20 mg/kg.

Parameter	Group (mg/kg/week)	Day 1				Day 22			
		Male		Female		Male		Female	
		Mean (SD)	Ratio	Mean (SD)	Ratio	Mean (SD)	Ratio	Mean (SD)	Ratio
C_{max} (µg/mL)	CT-P10 (20)	650 (331)	1.1	529 (56)	1.0	991[1] (-)	1.3	737 (189)	0.6
	MabThera® (20)	566 (133)		508 (55)		777[1] (-)		1230[2] (-)	
AUC_{0-168h} (µg.h/mL)	CT-P10 (20)	30700 (2300)	0.9	32500 (5200)	0.94	57600[1] (-)	1.6	28800 (9200)	0.35
	MabThera® (20)	34200 (5200)		34500 (2800)		37000[1] (-)		81500[2] (-)	

[1] Derived from only 2 animals and standard deviation was not calculated
[2] Derived from 1 animal only

Maximum serum concentrations (Cmax) and the areas under the serum concentration-time curves during a 168-hour dosing interval (AUC0-168h) of CT-P10 or Mabthera on Day 1 and Day 22

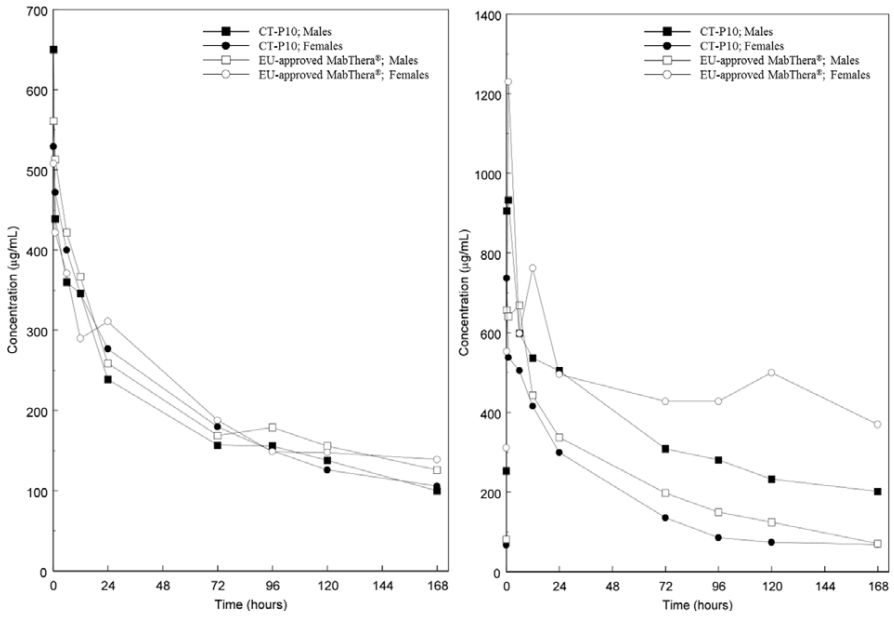


Figure 3: Mean Serum Concentrations of CT-P10 and Mabthera on Day 1 and Day 22 of Weekly Intravenous (Bolus) Administration to Male and Female Cynomolgus Monkeys at a Dose of 20 mg/kg/week.

2.2.4. Toxicology

Single dose toxicity

No comparative single-dose toxicity study was submitted.

Repeat dose toxicity

Key Parameters in the toxicokinetic study described under Pharmacokinetics were Clinical condition, bodyweight, ophthalmoscopy, body temperature, electrocardiography, haematology, blood chemistry, toxicokinetics, immunogenicity, immunophenotyping and pharmacodynamics, urinalysis, organ weight, macropathology and histopathology.

Key Findings Once-weekly administration of CT-P10 to cynomolgus monkeys for 5 weeks in female and 6 weeks in male produced no adverse toxicological findings and with the exceptions of the 2 decedents in animals receiving Mabthera responded to treatment in a generally similar manner.

Two deaths were reported for animals dosed with Mabthera (one female on Day 29 and one male on Day 36) receiving MabThera. Following the 4th dose (Day 22) effects reported (one female) included hunched posture, underactivity, piloerection, body tremors and bruising and/or swelling on the wrists, ankles, face, muzzle, shoulders and tail with additional findings after the 5th dose (Day 29) including vomiting, unresponsiveness, salivation, partially closed eyelids and unsteadiness. The animal was administered oxygen to regain consciousness and briefly showed recovery, but further deterioration prompted the early sacrifice of this animal. Haematology data (Day 24 and 28) revealed low haematocrit, haemoglobin and red blood cell counts for this animal. In contrast to the lower white blood cell counts observed on Day 3 and 24 and low platelet count on Day 24, a significant increase in these cell types was shown on Day 28. At necropsy pale kidneys were observed and with higher weight. Liver and spleen weights slightly higher than control were also recorded. The only clinical

findings in the remaining animals receiving Mabthera was piloerection for 1 male on Day 1 and vomiting for 1 female on Day 22.

There were no clear effect on bodyweight and temperature for animals receiving treatment with CT-P10 or MabThera over the treatment period. Also, there were no treatment related finding in ophthalmoscopy and electrocardiography.

Anti-drug antibody determination follows a multi-tiered assay approach - screening, confirmation and neutralisation assay. In the screening step, results were segregated as to whether they were below the cut point (reported as negative) or equal to or above the cut point (potentially positive). Of the 53 samples analysed, 4 samples for anti-CT-P10 and 6 samples for anti-Mabthera provided positive results (Screening Analysis), all the samples were confirmed positive during immunocompetition analyses (Confirmatory Analysis).

The determination of neutralising anti-drug antibodies in 17 cynomolgus monkey serum samples (10 positive with their corresponding 7 pre-treatment samples) analysed after receiving CT-P10/Mabthera was carried out. Of 10 positive samples, 4 samples from 3 animals for anti-CT-P10 (2 female at Week 7 and 1 male at Day 22 and Week 8) and 5 samples from 3 animals for anti-Mabthera (1 female at Day 22 and Week 7, 1 female at Day 22 and Day 29 terminal sporadic sample and 1 male at Day 22) were tested positive. One sample for anti- Mabthera (1 male at Week 8) was tested negative despite screening positive. Pre-treatment samples were negative. The neutralising anti-drug antibodies values were of a similar magnitude for those testing positive for either CT-P10 or Mabthera.

The total number of B-cells in the peripheral blood was significantly reduced for both compounds, consistent with the expected pharmacological activity of rituximab. After 14 days recovery B-cells increased slightly but reversal was not complete. The total number of NK cells appeared to decrease in the peripheral blood of females treated with CT-P10 but not in males or either sex receiving Mabthera. The total number of B-cells in the spleen, lymph node and bone marrow were also very reduced, and more evident in the lymph node. No other changes were observed in these lymphoid tissues. Immunophenotyping results were similar between animals administered CT-P10 or Mabthera, with lower than control and pre-treatment B-cell numbers observed in the peripheral blood, spleen, lymph nodes and bone marrow. The significance of the observed decrease in NK cell numbers in the peripheral blood of females receiving CT-P10 is unclear, and was the only difference noted between the 2 treatments.

Decrease in total and differential white blood cell counts was observed for animals receiving CT-P10 or Mabthera after the first dose, with the effect predominantly due to lower lymphocyte counts (0.42-0.5 X control for both sexes receiving CT-P10 or Mabthera). During Week 4, lower lymphocyte, neutrophil, eosinophil and basophil counts were recorded for females receiving CT-P10 or Mabthera (total counts 0.63 X and 0.5 X control for CT-P10 and Mabthera respectively). For males, the only significant difference from controls was lower neutrophil counts for animals receiving Mabthera (0.48 X control). In week 7 for females and week 8 for males haematological assessment (2 weeks after the last dose) the effects on white blood cells were not observed. Slightly lower group mean lymphocyte populations for females receiving CT-P10 and lower neutrophil counts for males receiving Mabthera were observed, but were restricted to one sex.

Low cholesterol levels was seen in females receiving CT-P10 on Day 3 and in Week 7 (0.82 and 0.78 X respectively) and to a lesser extent for females receiving Mabthera in Week 7 (0.86 X control) finding considered to have no toxicological significance. In Week 8 low phosphorus levels in males were reported for both compounds and only slight reduction was seen on day 3 (0.84 X control) but without statistical significance.

At the end of the treatment (Week 7 for females and Week 8 for males)higher organ weight was seen in female kidneys for both compounds (1.2 X and 1.3 X control respectively), and concomitant slightly high individual thymus weights for both sexes and compounds.

At the end of the treatment period, histopathologic changes considered to be related to treatment with CT-P10 were seen in the mesenteric lymph nodes and spleens of males and females. Changes related to treatment with Mabthera were also seen in the mesenteric lymph nodes of males and females but only in the spleens of males

There were no treatment-related effects on body weight, urinalysis, ophthalmology, body temperature, electrocardiography, macroscopic pathology, or injection site assessments (gross and histopathological assessments).

Genotoxicity

No genotoxicity studies have been submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been submitted as it is not a requirement for biosimilar products (see discussion on non-clinical aspects).

Reproduction Toxicity

Tissues from reproductive organs were evaluated in terms of macroscopic and microscopic histopathology in the 8-week repeat-dose toxicity study. Lower group mean uterus and cervix weights were recorded for treated female animals, but were largely attributable to a high value in the control group. No treatment-related histopathology changes were noted in reproductive organs. However studies regarding safety reproduction toxicology are not required for non-clinical testing of biosimilars.

Toxicokinetic data

See study resultsdescribed above.

Local Tolerance

Local tolerance at the injection site was assessed in the repeat-dose toxicity study as part of the gross pathology and histopathology evaluations. In the 8-week repeat-dose toxicity study, there were no toxicologically significant differences in injection site findings between treatment groups.

Other toxicity studies

No other toxicity studies have been performed. Similarity analyses of antigenicity and immune function, such as ADCC and CDC have been assessed in the *in vitro* PD studies.

2.2.5. Ecotoxicity/environmental risk assessment

The Applicant provided a justification for not submitting any environmental risk assessment studies based on the fact that Blitzima is a protein and therefore unlikely to pose a significant risk to the environment which is in

accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.2.6. Discussion on non-clinical aspects

The comparability assessment between CT-P10 and MabThera was carried out in accordance with EMA guideline (EMA/CHMP/BMWP/403543/2010). In this regard, potential difference in biological activity (see Quality aspects) was evaluated in *in vitro* relevant assays by each product. They comprised binding to target antigen (CD20); binding to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcRII and FcRIII), FcRn and complement (C1q); Fab-associated functions; and Fc-associated functions (ADCC, CDC and complement activation). No significant differences were reported in the above mentioned parameters.

Given the absence of in vitro biological difference, no in vivo studies should have been considered necessary (EMA/CHMP/BMWP/403543/2010). However, planning for MAA submissions in non-EU countries, the Applicant conducted an in vivo pharmacodynamic study in cynomolgus monkeys, which resulted in no difference between CT-P10 and MabThera in terms of pharmacodynamic actions.

The absence of studies into distribution, metabolism, excretion and drug-drug interactions was consistent with CHMP guidance (EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies). Furthermore studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars (See EMEA/CHMP/BMWP/42832/2005 Rev1)

The kinetics data was obtained from one 8-week repeat-dose intravenous toxicity study and toxicokinetic study with CTP10 and MabThera in cynomolgus monkey. Three animals per group were allocated. The C_{max} values of CT-P10 in monkeys on day one were similar to those values observed in the animals receiving MabThera although on Day 22 (with no evidence of anti-drug antibodies), a 40% lower C_{max} was reported in CT-P10 females while in males was 30% higher. Exposure levels were rather comparable on Day 1 although by day 22 was 1.6-fold higher in CT-P10 males and in females was about 65% lower than females receiving MabThera. Population pharmacokinetic analysis revealed that body surface area (BSA) and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender-related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment was not required. T_{max} was generally identified for both MabThera and CT-P10 at 15 min post dose.

Limited data were available for terminal half-life assessment (only one animal) on day one with a value of 83 hours. Values were much lower after 22 days (three animals) ranging from 26-45 h for CT-P10 group and 45 h for MabThera (one animal).

No genotoxicity or carcinogenicity studies were submitted for CT-P10 in line with the ICH S6 (R1) Guideline (2011) which states that such studies are generally inappropriate for biotechnology-derived products because large proteins, such as monoclonal antibodies, would not be expected to pass through cell membranes and interact directly with DNA or other chromosomal material. Moreover such studies are not needed for biosimilars (see EMEA/CHMP/BMWP/42832/2005 Rev1).

The product is exempted from the submission of environmental risk assessment studies based on the fact that it is a protein and therefore unlikely to pose a significant risk to the environment; this is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.2.7. Conclusion on the non-clinical aspects

Non-clinical studies were comprehensive and sufficient to establish comparability between CT-P10 and the reference product MabThera.

2.3. Clinical aspects

2.3.1. Introduction

Blitzima clinical is exactly the same as that submitted for the MAA of Truxima, thus the final assessment report adopted for Truxima is shown below:

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

  The clinical program supporting this MAA is summarised below in the following table.

Table: Summary of CT-P10 Phase 1 Clinical Trials

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} up to Week 24 between CT-P10 and Mabthera in patients with RA **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}) following the 2nd course treatment course	CT-P10 or Mabthera (1,000 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: 154 CT-P10: 103 Mabthera: 51	Final CSR (up to 72 weeks) was 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 (1,000 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	Final CSR (up to 104 weeks) was completed

Protocol	Design	Objective(s)	Treatment	Status
			CT-P10 Maintenance: 38 CT-P10 Switch: 20	
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 refractory DLBCL **Secondary:** To evaluate initial efficacy, PK and PD of CT-P10	CT-P10 (375 mg/m^2 by IV infusion) co-administered with DHAP (dexamethasone [40 mg orally or IV], cytosine arabinoside [2,000 mg/m^2 IV], cisplatin [100 mg/m^2 IV infusion]) up to 2 cycles during Induction Therapy, if a patient is eligible for ASCT, 1 additional cycle will be administered during Additional Therapy. If a patient is ineligible for ASCT, additional 4 cycles will be administered during Additional Therapy. Enrolled: 1	Study terminated due to recruitment difficulties Synoptic study report available

ASCT: Autologous stem-cell transplantation, AUC_{0-last}: Area under the concentration-time curve from time zero to time of last quantifiable concentration, C_{max}: maximum serum concentration (after 2nd infusion), C_{min}: minimum serum concentration immediately before the 2nd treatment course, C_{trough}: Concentration before the 2nd infusion, DHAP: Dexamethasone, Cytosine, Arabinoside and Cisplatin, DLBCL: Diffuse large B-cell lymphomas, IV: intravenous, MTX: Methotrexate, PD: Pharmacodynamics, PK: Pharmacokinetics, RA: Rheumatoid arthritis

Table: Summary of CT-P10 Phase 3 Clinical Trials

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-last}, AUC_{0-inf} 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:** (Part 1) To assess the additional PK variables of CT-P10, Rituxan and Mabthera over the first 24 weeks; To evaluate the PD and safety of CT-P10, Rituxan and Mabthera over the first 24 weeks (Part 2) To evaluate the additional PK (up to Week 48), efficacy, PD, overall safety and biomarkers of CT-P10 compared with reference products	CT-P10 or Rituxan/ Mabthera (1,000 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 pre-defined safety criteria: each course consists of 2 infusions with a 2-week interval. MTX (7.5 - 25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week) will be coadministered. Enrolled: 372 **Part 1** CT-P10: 64 Mabthera: 60 Rituxan: 65 **Part 2 (Including patients from Part 1)** CT-P10: 161 Mabthera + Rituxan: 211 (Mabthera: 60, Rituxan: 151)	Ongoing The analysis of PK, PD, efficacy, safety and immunogenicity (over 24 weeks) was completed. Estimated final CSR (up to 76 weeks) completion: 4Q/2017

Protocol	Design	Objective(s)	Treatment	Status
CT-P10 3.3 (PK similarity/ Therapeutic noninferiority)	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 Rituxan at Core Cycle 4 (Week 9-12) (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 over 8 cycles of Core Study Period **Secondary:** (Part 1 & 2) To evaluate other PK parameters, additional efficacy, PD, overall safety and biomarkers of CT-P10 compared with Rituxan	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** Enrolled and randomised: 121 CT-P10: 59 Rituxan: 62 **Part 2** Total 134 planned, including patients from part1.	Ongoing The analysis of PK, efficacy, safety and immunogenicity up to Core Cycle 4 (12 weeks) was completed. Estimated final CSR (up to 3 years) completion: 4Q/2019

[1]Patients from Rituxan and Mabthera groups will be combined as a reference group for the Part 2 analyses.
AFL: advanced follicular lymphoma, AUC_{0-inf}: Area under the serum concentration-time curve covering both infusion, time zero to infinity, AUC_{0-last}: Area under the concentration-time curve from time zero to time of last quantifiable concentration, AUC_{tau}: area under the serum concentration-time curve at steady state, C_{max}: maximum serum concentration (after 2nd infusion), $C_{max,SS}$: maximum serum concentration at steady state, CR: Complete response, CRP: C-reactive protein, CRu: Unconfirmed complete response, CSR: Clinical study report, CVP: Cyclophosphamide, Vincristine and Prednisone, DAS28: Disease activity score using 28 joint counts, IV: intravenous, IWG: International Working Group, LTBFL: Low-tumour-burden follicular lymphoma, MTX: Methotrexate, ORR: Overall response rate, PD: Pharmacodynamics, PK: Pharmacokinetics, PR: Partial response, RA: Rheumatoid arthritis

2.3.2. Pharmacokinetics

Pharmacokinetic parameters were measured in studies CT-P10 1.1. and CT-P10 3.2.

Analytical methods

CT-P10 and Mabthera are quantitatively measured directly from human serum using an electrochemiluminescent (ECL) immunoassay following a 1:25 dilution in assay buffer containing 3 % BSA, human serum samples containing CT-P10 or rituximab.

STUDY CT-P10 1.1

This was a Phase 1, randomized, controlled, multicenter, 2-arm, parallel-group, double-blind study to demonstrate the equivalence of CT-P10 to MabThera with respect to the pharmacokinetic profile in patients with rheumatoid arthritis (RA). For study description see Clinical efficacy.

The primary PK parameters were:

- AUC_{0-last}: calculated using the linear trapezoidal rule over both infusions of the first treatment course from the start of the 1st infusion to the last quantifiable concentration
- C_{max}: calculated after the second infusion of the Core Study Period

Other PK parameters were C_{max} (after first infusion in the Core Study Period), T_{max} (both after first and second infusion in the Core Study Period), C_{trough} (prior to second infusion in the Core Study Period), V_d, CL, and $t_{1/2}$ (after second infusion in the Core Study Period), C_{min} (prior to Extension Study Period), C_{trough} (prior to second infusion in the Extension Study Period).

The PK sampling time points were selected based on the mean rituximab terminal elimination half-life ($t_{1/2}$) ranging from 17 to 23 days except for CLL indication with 32 days (Mabthera SmPC 2015). The choice of an interval of 24 weeks would correspond to approximately 7 half-lives (see above the median terminal half-life) and would allow covering at least 80% of the AUC.

A total of 154 patients were randomly assigned to study drug: 103 patients and 51 patients in the CT-P10 and MabThera treatment arms, respectively. Of these, 153 patients initiated study drug treatment due to one patient in the CT-P10 treatment arm having poor venous access.

Although 137 patients completed the study, 141 patients were used since the following criteria were satisfied: sufficient blood concentration data was available to compute at least 1 of the PK parameters up to Core Week 16; and a pre-dose sample at their Core Week 2 (Day 14) visit was available. This population was the primary population for the summary and analysis of PK data.

Overall, demographic characteristics were well balanced between the 2 treatment arms. The mean age of the population was 50 years and there were fewer male patients (12%) than female patients (88%). The majority of patients were white (68). The mean body mass index (BMI) was 27.The duration of RA disease was similar between the 2 treatment arms: 11 years in the CT-P10 arm and 10 years in the MabThera arm. Most patients had received only one prior TNF inhibitor (84%) and the reason for stopping it was mainly therapeutic failure (92%). The most frequently used products were adalimumab, infliximab, and etanercept. The duration of previous anti-TNF use was 21 months on average (See Clinical efficacy section).

All patients took MTX and folic acid during the study, as per the study design and requirements. The mean ± SD dose of MTX taken during the study was similar between the 2 treatment arms: 15.34 ± 4.82 mg/week and 15.59 ± 4.32 mg/week in the CT-P10 and MabThera arms, respectively.

All patients also took analgesics, systemic corticosteroids (100% in the CT-P10 and 98% in the reference product arms, respectively), antihistamines (88% and 90%, respectively), and other anti-inflammatory/antirheumatic products (80% and 82%, respectively).

Table 19 Results for the primary endpoints, $AUC_{0\text{-last}}$ and C_{max}, in the Core Study Period.

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 new PK analysis using all concentration data available from all patients having been administered 2,000 mg of rituximab was conducted which showed that the 90%CIs of all the PK parameters were within the acceptance limits with ratios close to 100.

Secondary PK Parameters

Serum secondary PK parameters for rituximab are summarized up to Week 24 in the Core Study Period for the PK population in the following table.

Table 15: PK Parameters of CT-P10 and MabThera

Parameter	CT-P10 1000 mg (N=96)		MabThera® 1000 mg (N=45)	
$C_{max,\ 1}$ (µg/mL)	n=96	381.01 (18.9)	n=45	396.24 (22.0)
$T_{max,\ 1}$ (h)*	n=96	5.03 (3.43, 24.00)	n=45	5.00 (4.22, 6.42)
T_{max} (h)*	n=96	3.86 (2.10, 24.00)	n=45	3.83 (2.25, 5.25)
$T_{1/2}$ (day)	n=94	14.91 (24.9)	n=44	14.51 (21.6)
$AUC_{0\text{-t}}$ (day•µg/mL)	n=96	2206.07 (22.9)	n=45	2258.85 (22.1)
$AUC_{0\text{-}\infty}$ (day•µg/mL	n=94	8442.54 (27.1)	n=44	8405.09 (26.5)
$AUC_{t\text{-}\infty}$ (day•µg/mL)	n=94	6228.61 (30.4)	n=44	6160.01 (30.0)
CL (L/day)	n=94	0.26 (32.4)	n=44	0.26 (30.3)
V_d (L)	n=94	5.33 (26.4)	n=44	5.20 (25.0)
V_{ss} (L)	n=94	6.15 (22.0)	n=44	6.13 (23.3)
C_{trough} (µg/mL)	n=96	85.06 (88.7)	n=45	80.30 (29.4)

Tertiary PK Parameters

The tertiary PK endpoints were C_{min} immediately before the start of first infusion in the Extension Study Period and C_{trough} prior to the second infusion of the Extension Study Period.

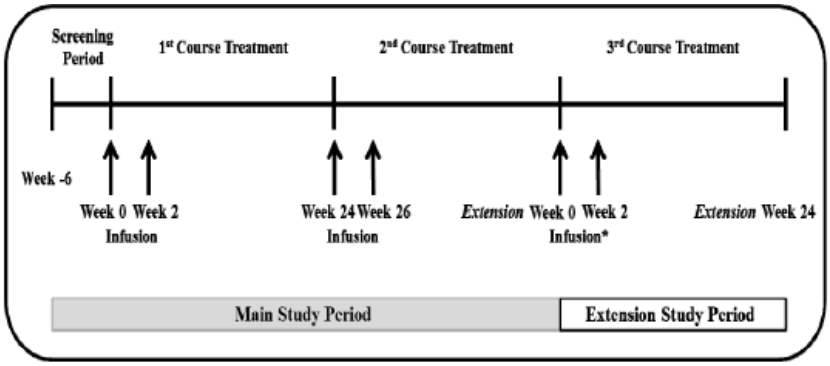
The geometric means for C_{min} were 0.04 µg/mL and 0.03 µg/mL and for C_{trough} were 71.12 µg/mL and 78.36 µg/mL in CT-P10 and Mabthera groups, respectively.

Additional PK parameters analysed from the Extension Study, C_{max}, after the first infusion were: ($C_{max,\ 1}$) (286.47 µg/mL and 331.86 µg/mL in CT-P10 and Mabthera groups, respectively) and C_{max} after the second infusion in the Extension Study Period (424.12 µg/mL and 431.07 µg/mL in CT-P10 and Mabthera groups, respectively).

STUDY CT-P10 3.2;

This ongoing study was a randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective, Phase 3 study was designed to demonstrate similar pharmacokinetics in terms of ($AUC_{0\text{-}last}$), AUC from time 0 extrapolated to infinity over both doses of the first treatment course ($AUC_{0\text{-}\infty}$), and observed maximum concentration (C_{max}) after the second infusion between CT-P10, Rituxan, and MabThera in patients with active RA who were concomitantly treated with methotrexate (MTX) and folic acid during the first treatment course (over the first 24 weeks). Change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP]) at Week 24 was the primary efficacy parameter.

Overall Study Schematic



* The third treatment course was initiated between Week 48 and Week 52 of the entire study period based on the results assessed within 8 weeks from Extension Week 0.

Each course consisted of 2 infusions: a dose of 1,000 mg of CT-P10, Mabthera or Rituxan (IV) separated by a 2-week interval. In the third treatment course (1 additional course in the Extension Study Period), patients who received Rituxan in the Main Study Period will be re-randomised to either the Rituxan or CT-P10 treatment groups and patients who received Mabthera in the Main Study Period will be switched to CT-P10 while patients who received CT-P10 will remain in CT-P10 group.

The main criteria for inclusion were male or female patients between 18 and 75 years old, inclusive, who had been diagnosed with rheumatoid arthritis according to the revised 1987 American College of Rheumatology (ACR) classification criteria for at least 6 months prior to randomization.

The following PK Parameters were determined as primary and secondary endpoints in Part 1 and Part 2.

Table: Endpoints of Part 1 and Part 2 of CT-P10 3.2

		Part 1 (189 patients)			Part 2 (372 patients)	
		CT-P10 (64 patients)	MabThera® (60 patients)	Rituxan® (65 patients)	CT-P10 (161 patients)[1]	MabThera® + Rituxan® (211 patients)[2]
PK	Primary	$AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} over the first 24 weeks			N/A	
	Secondary	$AUC_{0\text{-t}}$, V_d, CL, $T_{1/2}$, $C_{max,1}$, T_{max}, C_{min} and C_{trough} over the first 24 weeks			C_{max}, T_{max}, C_{min} and C_{trough} over the 24 weeks	
PD	Secondary	B-cell kinetics; CRP; ESR; RF; anti-CCP antibodies				
IM	Secondary	ADA; NAb				

A total of 372 male and female patients with RA were enrolled; 189 patients were included in Part 1 and 1:1:1 randomised into the CT-P10, Mabthera and the Rituxan group.

The PK population for the first treatment course consisted of all patients who received at least 1 full dose (1000 mg) of study drug and provided at least 1 post-treatment PK concentration results during the first treatment course.

PK results

Table 16: Co-primary PK parameters results from data including outliers.

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		

The Applicant also has conducted statistical PK analysis for additional secondary PK parameters, AUC_{0-t}, AUC_{t-inf}, C_{max} and C_{trough} after 1st infusion. The 90% CI of the ratio of geometric LS means for additional secondary PK parameters in PK population are presented below.

Table: Statistical PK Analysis for Additional Secondary PK Parameters

Parameter	Comparison	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
AUC_{0-t} (h•µg /mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	62	43356.29	88.51	82.00 - 95.53
		Reference	59	48984.76		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	62	43356.29	96.48	89.50 -104.00
		Reference	63	44939.02		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	59	48984.76	109.00	100.95 -117.70
		Reference	63	44939.02		
AUC_{t-inf} (h•µg /mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	59	119108.77	90.14	79.85 - 101.76
		Reference	56	132136.70		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	59	119108.77	100.68	89.46 - 113.31
		Reference	62	118301.30		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	56	132136.70	111.70	98.99 - 126.03
		Reference	62	118301.30		
$C_{max,1}$ (µg/mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	62	305.77	87.33	81.61 - 93.44
		Reference	59	350.15		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	62	305.77	95.70	89.54 - 102.28
		Reference	63	319.53		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	59	350.15	109.58	102.38 - 117.30
		Reference	63	319.53		

Parameter	Comparison	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
C_{trough} (µg/mL)	CT-P10 (Test) vs. MabThera® (Reference)	Test	62	66.51	93.04	80.33 -107.76
		Reference	59	71.48		
	CT-P10 (Test) vs. Rituxan® (Reference)	Test	62	66.51	93.09	80.57 - 107.55
		Reference	63	71.45		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	59	71.48	100.05	86.32 - 115.98
		Reference	63	71.45		

Secondary PK Parameters

Table 17. Mean secondary PK endpoints in Part 1 for the CT-P10, Mabthera and Rituxan groups

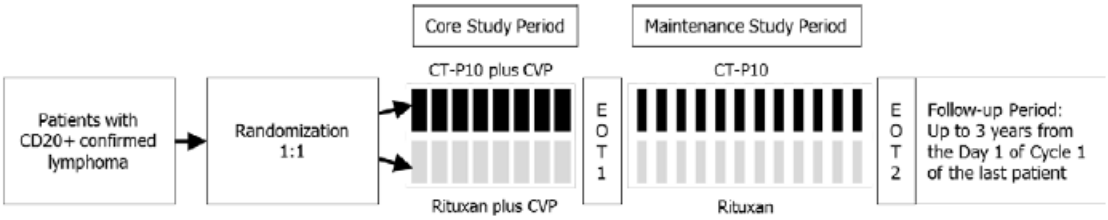
Parameter	CT-P10 1000 mg (N=62)		MabThera® 1000 mg (N=59)		Rituxan®1000 mg (N=63)	
$AUC_{0\text{-last}}$ (h•µg/mL)	n=62	188400.03 (34.7)	n=59	199754.50 (34.1)	n=63	184121.66 (35.6)
$AUC_{0\text{-inf}}$ (h•µg/mL)	n=59	184478.20 (30.6)	n=56	206484.59 (31.3)	n=62	187138.88 (34.1)
$AUC_{0\text{-t}}$ (h•µg/mL)	n=62	48726.70 (25.9)	n=59	54419.65 (23.5)	n=63	49979.93 (28.6)
C_{max} (µg/mL)	n=62	425.05 (22.5)	n=59	474.19 (21.2)	n=63	423.07 (29.3)
$C_{max,1}$ (µg/mL)	n=62	347.13 (22.3)	n=59	394.25 (20.2)	n=63	358.27 (24.2)
$C_{min,\ week24}$ (µg/mL)	n=54	0.3573 (163.1)	n=56	0.4660 (162.2)	n=57	0.4460 (158.8)

Parameter	CT-P10 1000 mg (N=62)		MabThera® 1000 mg (N=59)		Rituxan®1000 mg (N=63)	
C_{trough} (µg/mL)	n=62	75.14 (66.4)	n=59	81.76 (67.3)	n=63	83.17 (77.2)
V_d (mL)	n=59	5971.0859 (23.3)	n=56	5531.3226 (22.1)	n=62	6228.6344 (40.1)
CL (mL/h)	n=59	11.9588 (33.0)	n=56	10.6950 (32.7)	n=62	12.5561 (49.9)
$T_{1/2}$ (day)	n=59	15.04 (20.0)	n=56	15.19 (20.4)	n=62	15.65 (23.6)
T_{max} (h)[1]	n=62	339.9 (5.2, 435.3)	n=59	339.3 (4.5, 346.5)	n=63	339.3 (4.5, 364.4)

Also, secondary PK parameters in Part 2, which are t_{max}, C_{max}, C_{min} and C_{trough} are similar for the CT-P10 and the reference products groups up to Week 24.

STUDY CT-P10 3.3

This study was a Phase 1/3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with cyclophosphamide, vincristine and prednisone (CVP) in patients with Advanced Follicular Lymphoma (AFL).



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

The main criteria for inclusion was 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), at least 1 measurable tumor mass that had not previously been irradiated, confirmed CD20+ lymphoma, Ann Arbor stage III or IV disease,

Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate bone marrow, hepatic, and renal function reserve.

Patients were to receive up to 8 cycles of study treatment (duration of each cycle was 21 days) in the Core Study Period and 12 cycles of study treatment (duration of each cycle was 2 months) in the Maintenance Study Period.

Up to Core Cycle 4 (over 12 weeks), CT-P10 or Rituxan 375 mg/m^2 were administered as an IV infusion on Day 1 of each cycle, and CVP (cyclophosphamide 750 mg/m^2 IV, vincristine 1.4 mg/m^2 [up to a maximum of 2 mg] IV, prednisone 40 mg/m2 oral) were administered during the Core Study Period. CT-P10 or Rituxan (375 mg/m^2 IV) was administered alone as maintenance in patients who have a response during the Core Study Period.

One hundred twenty-one (121) patients were randomly assigned to study drug and initiated core study treatment (59 patients and 62 patients in the CT-P10 and Rituxan treatment groups, respectively).

The majority of patients in each treatment group completed up to and including Core Cycle 4 in the study (55 [93.2%] patients and 58 [93.5%] patients in the CT-P10 and Rituxan treatment groups, respectively). The most frequently reported reason for discontinuation from the Core Study Period was progressive disease (2 [3.4%] patients and 1 [1.6%] patient in the CT–P10 and Rituxan treatment groups, respectively). One patient died due to AE (reported as tumor lysis syndrome) in the CT-P10 treatment group. In addition, another patient who entered follow-up period died due to progress disease.

The PK population was defined as all patients who received at least 1 dose (full) of study drug (CT-P10 or Rituxan) and who had at least 1 post-treatment PK result and who did not have any major protocol deviation (Section 9.7.1.3) that was relevant to the PK endpoint.

PK results

Table 18: Analyses of primary serum PK parameters (AUC_{tau} and $C_{max,ss}$) CT-P10 and Rituxan at Core Cycle 4 (ANCOVA) in the PK population (Part 1) including outliers.

Parameter	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of the Ratio (%)
AUC_{tau} (h•µg/mL)	CT-P10 375mg/m^2	55	30658.51	95.32	81.03 - 112.14
	Rituxan® 375mg/m^2	58	32162.68		
$C_{max,ss}$ (µg/mL)	CT-P10 375mg/m^2	55	225.88	101.38	93.49 - 109.94
	Rituxan® 375mg/m^2	58	222.81		

AUC_{tau}: area under the serum concentration-time curve at steady state, $C_{max,ss}$: The observed maximum serum concentration following drug administration at steady state, LS: Least Squares, PK: Pharmacokinetics

Table 19: Supportive analysis including and excluding outliers.

Parameter	Treatment	n	Geometric LS Mean	Ratio (%) Of Geometric LS Means	90% Confidence Interval Of The Ratio
AUC_{tau} (h*ug/mL)	CT-P10	49	40279.44	95.10	84.24 - 107.36
	Rituxan	54	42355.79		
$C_{max,ss}$ (ug/mL)	CT-P10	49	256.63	101.23	93.81 - 109.25
	Rituxan	54	253.50		

Table 20: Mean (%CV) Secondary PK Parameters of CT-P10 and Rituxan in PK Population (Part 1, Up to Core Cycle 4 at steady state[Week 12])

Parameter	CT-P10 375 mg/m² (N=59)		Rituxan® 375 mg/m² (N=62)	
Core Cycle 1				
C_{max} (µg/mL)	n=59	173.67 (40.843)	n=62	209.75 (21.801)
C_{trough} (µg/mL)	n=59	20.248 (199.656)	n=61	28.400 (166.410)
Core Cycle 2				
C_{max} (µg/mL)	n=58	206.27 (32.484)	n=60	225.94 (31.858)
C_{trough} (µg/mL)	n=57	31.312 (59.715)	n=59	45.416 (91.989)
Core Cycle 3				
C_{max} (µg/mL)	n=56	228.94 (30.296)	n=58	246.81 (31.515)
C_{trough} (µg/mL)	n=55	50.593 (71.720)	n=58	60.843 (80.435)
Core Cycle 4				
$C_{trough,ss}$ (µg/mL)	n=55	60.395 (44.850)	n=58	63.915 (49.569)
$C_{av,ss}$ (µg/mL)	n=55	110.53 (30.688)	n=58	118.39 (30.830)
$T_{max,ss}$ (h)[1]	n=55	3.750 (2.25, 24.25)	n=58	3.350 (2.37, 26.43)
V_{ss} (L)	n=48	4.6566 (24.454)	n=47	4.5665 (26.721)
CL_{ss} (L/day)	n=55	0.420 (131.095)	n=58	0.329 (82.826)
$T_{1/2}$ (h)	n=48	279.39 (30.305)	n=47	292.15 (22.402)
MRT (h)	n=48	388.03 (35.968)	n=47	410.56 (25.886)
PTF_{ss}	n=55	2.555 (83.051)	n=58	2.059 (36.597)
λz (/h)	n=48	0.00303 (72.495)	n=47	0.00251 (27.454)

2.3.3. Pharmacodynamics

Mechanism of action

Rituximab is a chimeric murine/human IgG1 monoclonal antibody with murine heavy and light-chain variable regions (Fab domain) and human kappa (light chain) and gamma-1 (heavy chain) constant regions (Fc domain). The biological function of rituximab is mediated by the two functional domains of the antibody: the Fab domain of rituximab binds to the CD20 antigen on B-cells and the Fc domain can recruit immune effector functions to mediate B-cell lysis. The proposed mechanisms by which rituximab promotes B-cell lysis, supported by in vitro data, are antibody-dependent cellular cytotoxicity (ADCC) by NK cells, antibody-dependent cellular phagocytosis (ADCP) by macrophages and neutrophils, complement-dependent cytotoxicity (CDC) and apoptosis induced by activation of signalling pathways. In summary, the primary mechanism of action of rituximab can be attributed to Fc and/or F(ab)2 functionality as either F(ab)2 mediated (induction of apoptosis of CD20+ B-cells), or Fc mediated (ADCC, ADCP, CDC).

All of these pathways are likely active in the clinical setting but their relative contribution to the overall depletion of B-cell numbers and therapeutic efficacy of rituximab is unclear. The extent to which each of these mechanisms of action can contribute to B-cell elimination in autoimmune and lympho-proliferative diseases depends on a number of factors, including CD20 expression, tumour localisation, complement levels, free plasma IgGs, the extent and status of tumour infiltration by immune effector cells such as NK cells, macrophages and neutrophils.

In addition to the four mechanisms described, evidence suggests that rituximab may induce an anti-tumour response by cytotoxic T lymphocytes. Rituximab-induced killing of malignant B-cells can result in release of tumour antigens into adjacent tissue causing local inflammation. Such an environment promotes the uptake of tumour-associated antigens by dendritic cells and cross-presentation to T-lymphocytes, providing the potential for cell-mediated immunity. The binding to CD20 is mediated via the Fab domain of rituximab and the Fc domain

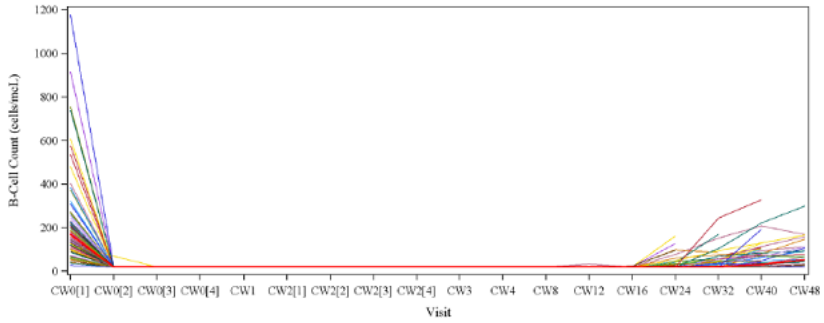
can recruit immune effector functions to mediate B-cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, antibody-dependent cellular cytotoxicity (ADCC) mediated by 1 or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells, and antibody-dependent cellular phagocytosis (ADCP).

Primary and Secondary pharmacology

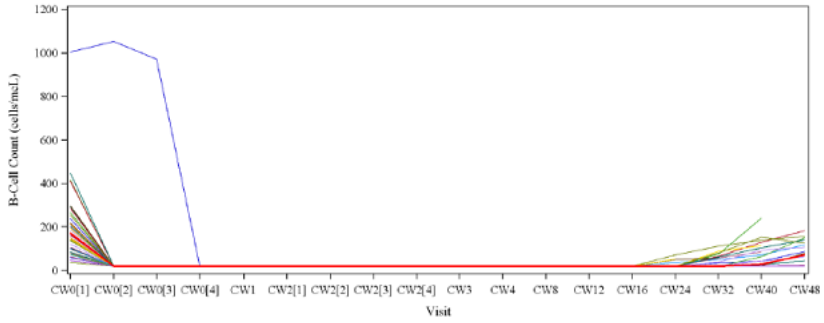
STUDY CT-P10 1.1 and CT-P10 1.3

The PD effect of rituximab on B-cell count (measured by flow cytometry), which directly reflects its activity, was evaluated in Study CT-P10 1.1 and its open-label extension CT-P10 1.3.

Figure 4: Spaghetti Plots of B-cell Counts up to Week 48 of Core Study Period in Study CT-P10 1.1: PD Population



(a) CT-P10 group



(b) MabThera® group

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

The mean baseline B-cell count was higher in the CP-T10 than in the MabThera arm. In all patients, the B-cell count was below LLoQ (20 cells/ µL) by the next time point, i.e. usually the end of the infusion, or 24 hours after the start of the infusion at the latest. Total depletion was observed in all patients for 16 weeks.

The proportion of patients achieving B-cell recovery (i.e. ≥lower limit of normal (LLN) of 110 cells/µL or at least 50% of the baseline value) was presented up to Core Week 48 in patients who did not receive a second treatment course (*post-hoc* analysis).

Table 2.7.2-11: Proportion of Patients Achieving B-cell Recovery in the Core Study Period of Study CT-P10 1.1: PD Population

Visit	CT-P10 1000mg (N=100)	MabThera® 1000mg (N=48)
Core Week 0	0/90	0/41
Core Week 3	0/92	0/43
Core Week 4	0/92	0/43
Core Week 8	0/92	0/43
Core Week 12	0/92	0/42
Core Week 16	0/93	0/43
Core Week 24	7/91 (7.7%)	1/41 (2.4%)
Core Week 32	10/73 (13.7%)	3/36 (8.3%)
Core Week 40	14/58 (24.1%)	6/29 (20.7%)
Core Week 48	10/30 (33.3%)	9/19 (47.4%)

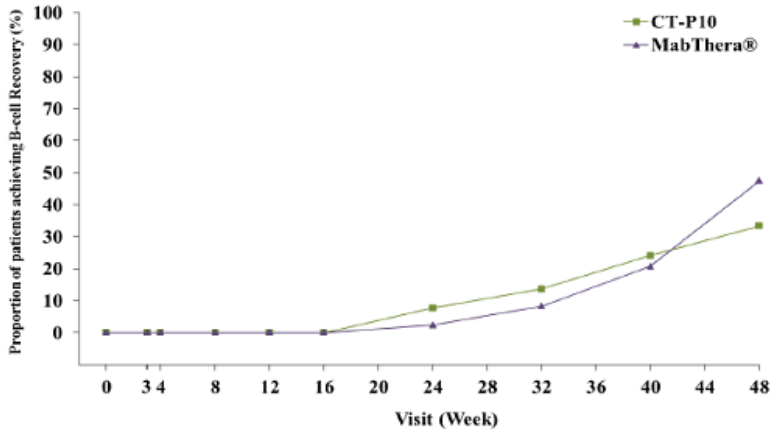


Figure 2.7.2-5: Proportion of Patients Achieving B-cell Recovery up to Week 48 of Core Study Period in Study CT-P10 1.1: PD Population

Figure 5: Time to event KM analysis in the all randomised/treated population

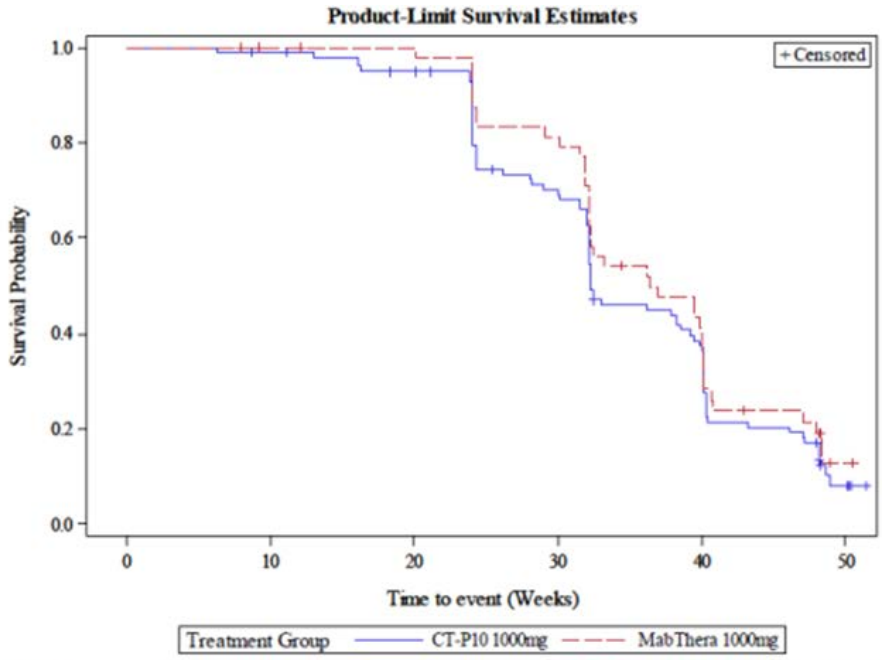


Figure 1: Time to Event Being First B-cell Value above LLoQ, Retreatment or Discontinuation for Lack of Efficacy Kaplan-Meier Curve in Study CT-P10 1.1: All-randomised/Treated Population

Figure 6: Patients Distribution by the Number of Treatment Courses Throughout the Studies CT-P10 1.1 and CT-P10 1.3: Safety Population

Treatment Group	Subgroup	Study CT-P10 1.1		Study CT-P10 1.3		Number (%) of Patients
		Core Study Period	Extension Study Period	Treatment Period 1	Treatment Period 2	
CT-P10/ CT-P10 Maintenance (N=102)	1	CT-P10				29 (28.4)
	2	CT-P10	CT-P10			35 (34.3)
	3	CT-P10		CT-P10		13 (12.7)
	4	CT-P10	CT-P10	CT-P10		24 (23.5)
	5	CT-P10	CT-P10	CT-P10	CT-P10	1 (1.0)
Subtotal		**102 (100.0)**	**60 (58.8)**	**38 (37.3)**	**1 (1.0)**	**102 (100.0)**
MabThera®/ CT-P10 Switch (N=51)	1	MabThera®				19 (37.3)
	2	MabThera®	MabThera®			12 (23.5)
	3	MabThera®		CT-P10		9 (17.6)
	4	MabThera®	MabThera®	CT-P10		11 (21.6)
Subtotal		**51 (100.0)**	**23 (45.1)**	**20 (39.2)**	**0**	**51 (100.0)**
Total		**153 (100.0)**	**83 (54.2)**	**58 (37.9)**	**1 (0.6)**	**153 (100.0)**

STUDY CT-P10 3.2

Initial results from study CT-P10 3.2, showed that B-cell counts from all patients, except 1 in CT-P10 group, decreased to below the LLoQ (20 cells/µL) immediately after the 1st infusion and then remained below this level up to Week 24 in the majority of patients in all treatment groups. Updated data over the main study period (up

to week 48) showed that study CT-P10 3.2 involved systematic retreatment at week 24, except for safety reasons (which occurred in 4 patients; 1%).

The proportion of patients that completed two treatment courses was 87% (CT-P10), 89% (Rituxan); 93% (MabThera). The main reason for discontinuation, especially for CT-P10, was withdrawal of consent.

KM time to event analysis of Part 1 (with the event being first B-cell value above LLoQ, or discontinuation for lack of efficacy, or disease progression excluding time to re-treatment,) showed a trend for earlier B-cell recovery with CT-P10 compared to MabThera and Rituxan. While the proportion of patients with B-cell recovery before week 48 was higher with Rituxan (31%) than CT-P10 (22%), it occurred in the majority of the cases at week 24 with Rituxan and at earlier time points with CT-P10. The proportion of patients with B-cell recovery was the lowest with MabThera (17%).

Table 7: Time to Event Being First B-cell Value above the LLoQ or Discontinuation due to Lack of Efficacy or Disease Progression excluding the time to retreatment in Study CT-P10 3.2: ITT Population - Part 1

	CT-P10 (N=64)	MabThera® (N=60)	Rituxan® (N=65)
Number of patients with event[1]	15 (23.4%)	11 (18.3%)	20 (30.8%)
First B-cell value above the LLoQ	14 (21.9%)	10 (16.7%)	20 (30.8%)
Discontinuation for lack of efficacy or disease progression	1 (1.6%)	1 (1.7%)	1 (1.5%)
Number of censored patients	49 (76.6%)	49 (81.7%)	45 (69.2%)

Figure 7: Time to event KM analysis – Part 1

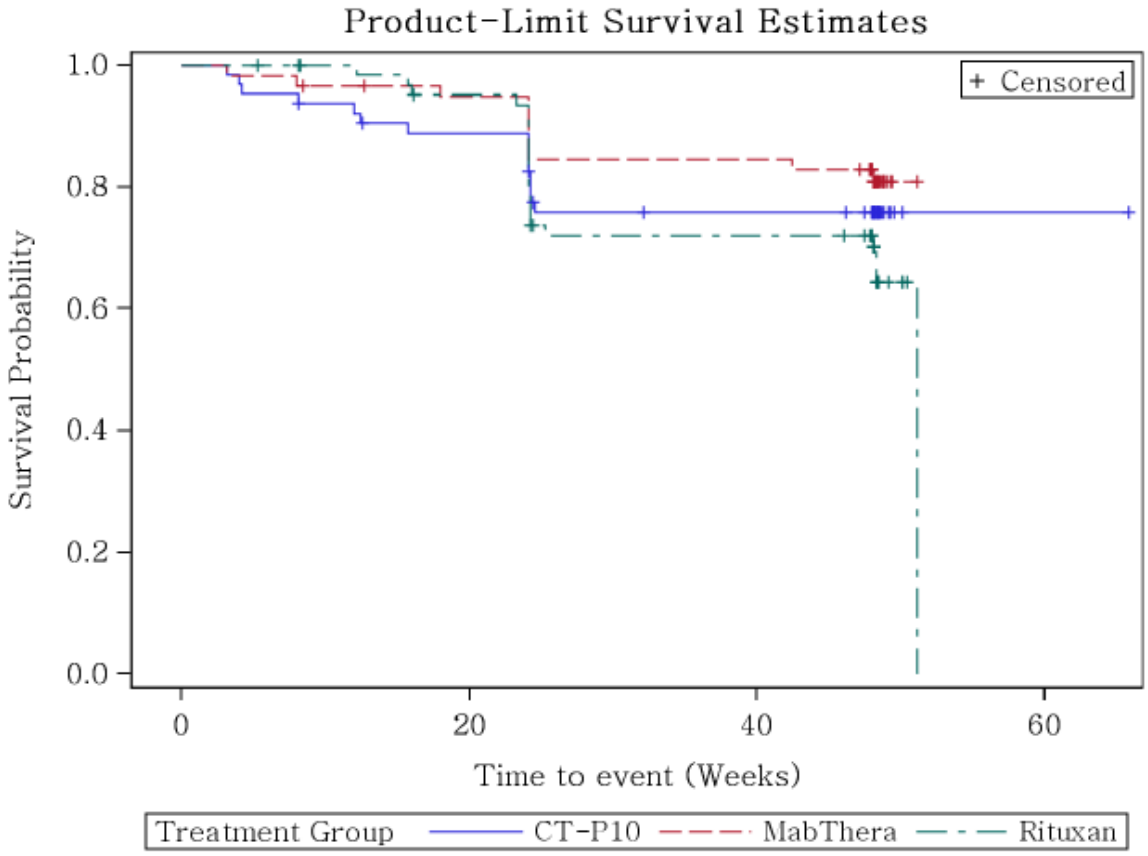
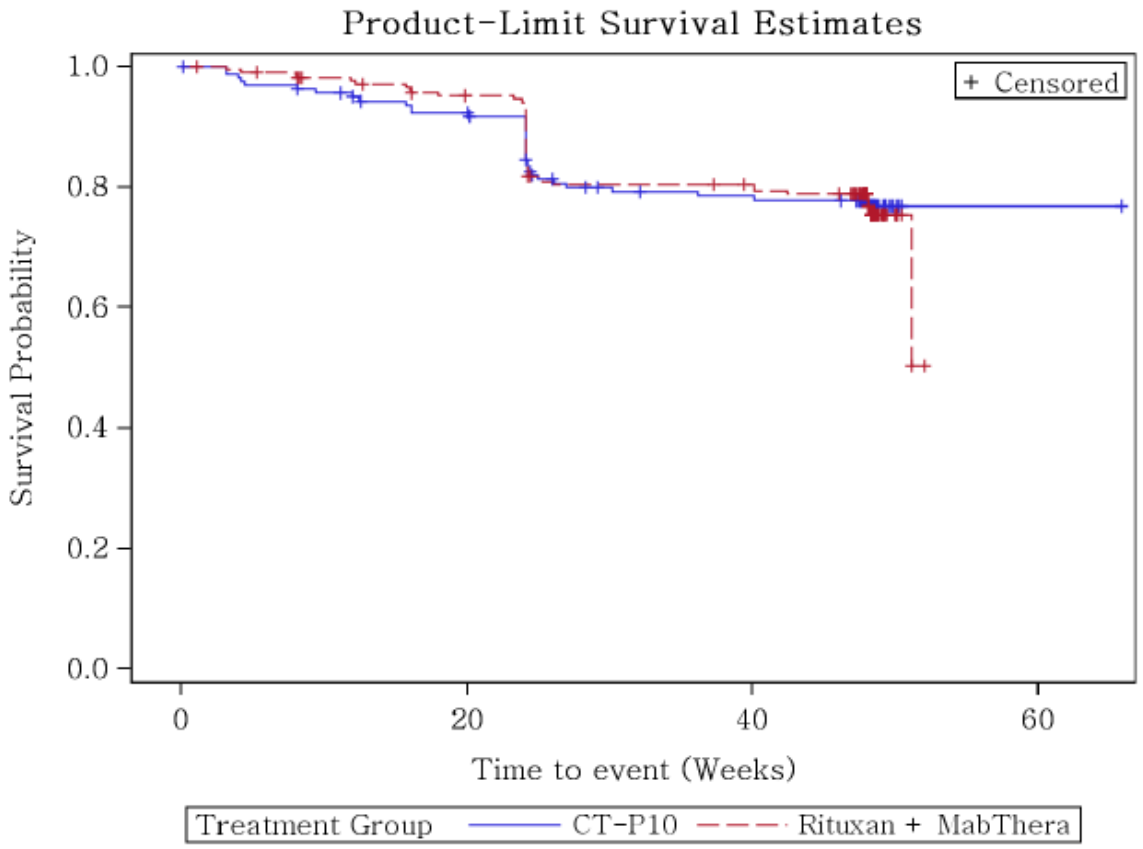


Table 3: Time to Event Being First B-cell Value above the LLoQ or Discontinuation due to Lack of Efficacy or Disease Progression excluding the time to retreatment in Study CT-P10 3.2: ITT Population - Part 2

	CT-P10 (N=161)	MabThera®+Rituxan® (N=211)
Number of patients with event[1]	35 (21.7%)	48 (22.7%)
First B-cell value above the LLoQ	34 (21.1%)	46 (21.8%)
Discontinuation for lack of efficacy or disease progression	2 (1.2%)	3 (1.4%)
Number of censored patients	126 (78.3%)	163 (77.3%)

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



STUDY CT-P10 3.3

Study CT-P10 3.3. performed in patients with AFL, showed median B-cell levels that decreased below the LLoQ (20 cells/µL) 1 hour after the end of infusion at Core Cycle 1 and remained at the LLoQ pre-dose levels at each subsequent cycle for the majority of patients up to and including Cycle 8 (over 24 weeks) in the Core Study Period. A similar trend was observed for mean B-cell counts in both treatment groups up to Core Cycle 8.

Table 1: Actual Values for B-cell Counts of CT-P10 and Rituxan®: PD Population (Part 2, Up to Core Cycle 8 [24 Weeks])

Visit (Time point)	CT-P10 375 mg/m² (N = 70)			Rituxan® 375 mg/m² (N = 70)		
	n	Median (25th, 75th)	Mean (±SD)	n	Median (25th, 75th)	Mean (±SD)
Baseline	56	92.5 (55, 216)	407.0 (±784.42)	57	62.0 (31, 139)	203.1 (±530.66)
Core Cycle 1 (1hr after EOI)	44	20 (20, 20)	47.0 (±164.38)	55	20 (20, 20)	21.4 (±5.85)
Core Cycle 2 (Pre-dose)	60	20 (20, 20)	69.0 (±265.21)	60	20 (20, 20)	78.5 (±373.96)
Core Cycle 3 (Pre-dose)	63	20 (20, 20)	24.8 (±28.68)	62	20 (20, 20)	20.2 (±1.91)
Core Cycle 4 (Pre-dose)	59	20 (20, 20)	20.6 (±4.05)	61	20 (20, 20)	20.0 (±0)
Core Cycle 5 (Pre-dose)	60	20 (20, 20)	20 (±0)	57	20 (20, 20)	20 (±0)
Core Cycle 6 (Pre-dose)	60	20 (20, 20)	20.2 (±1.68)	61	20 (20, 20)	20 (±0)
Core Cycle 7 (Pre-dose)	60	20 (20, 20)	20.1 (±0.52)	63	20 (20, 20)	20 (±0)
Core Cycle 8 (Pre-dose)	61	20 (20, 20)	20 (±0)	59	20 (20, 20)	20 (±0)

Note: Any value recorded below the LLoQ (20 cells/µL) or above ULoQ (2890 cells/µL) was set to the respective limit for this analysis. The baseline value is the last non-missing value, before the 1st infusion.
EOI: End-of-infusion, N: Number of patients randomised, n: Number of patients who have B-cell count results at each visit, PD: Pharmacodynamics

There were few patients whose B-cell counts fluctuated during the treatment cycles but most of the values decreased again. There were 3 patients in CT-P10 group who had B-cell counts of 23 cells/µL at Core Cycle 4, 33 cells/µL at Core Cycle 6 and 24 cells/µL at Core Cycle 7, respectively. All of these patients' B-cell counts decreased to LLoQ at subsequent cycles and showed overall responses up to Core Cycle 8. There were no patients showing B-cell recovery throughout 24-week study period.

Immunogenicity

The updated immunogenicity database in the CT-P10 clinical development programme consists of 666 RA and NHL patients. Of those patients with RA, 283 patients treated with CT-P10 and 262 patients treated with MabThera/Rituxan have been assessed for immunogenicity up to 104 weeks including 20 patients who were treated with both CT-P10 and MabThera in Study CT-P10 1.1 and its open-label maintenance study (CT-P10 1.3). In AFL patients, 70 patients treated with CT-P10 and 70 patients with Rituxan have been assessed for immunogenicity up to and including Core cycle 8 (over 24 weeks). In CT-P10 clinical development programme,

the presences of ADAs and/or NAbs were determined using state-of-art and validated immunoassays across the CT-P10 RA and AFL studies.

In Study CT-P10 1.1, the ADA incidence from week 24 onwards and the proportion of patients who seroconverted after 1-2 treatment courses were comparable in both treatment arms. However, there was a difference in the kinetic profile with ADAs detected earlier in the CT-P10 arm than in the MabThera arm: 10% vs. 2%, respectively, at week 16 (when considering only evaluable samples with low drug concentration).

There was one patient who had considerably higher level of ADA and NAb titre throughout the 1st and 2nd treatment courses in Study CT-P10 1.1. with no drug detectable in his serum and experienced, a moderate (grade 3) event of infusion related reaction after the 2nd infusion of the 2nd treatment course, however this patient continued in the study up to Extension Week 24 and showed moderate EULAR responses during both the 1st and 2nd treatment courses. Therefore the presence of ADA in this patient did not appear to have an overt impact on treatment efficacy and did not result in treatment discontinuation. Moreover most of the ADA positive responses were non-neutralizing in nature and did not have an overt clinical meaningful impact as demonstrated further in the analyses of PK, PD, efficacy and safety by ADA status or seroconversion status.

In Study CT-P10 1.1, a small numerical trend in the number of ADA positive patients at baseline 3/102 (22.5%) patients and 7/51 (13.7%) patients in the CT-P10 and MabThera groups, respectively, was observed and the ADA method was further optimised and modified following extensive investigations. In Studies CT-P10 3.2 and CT-P10 3.3 using a modified ADA method, reduced rates of baseline ADA positivity were observed and the ADA results were similar between the treatment groups in the Phase 3 studies.

In Study CT-P10 3.2, the immunogenicity rate at week 24, in the randomised part 1 of the study, the ADA incidence in the CT-P10 arm was 13.6% in the MabThera arm it was 27.6% and in the Rituxan arm 23.3%. One patient had a high titre and neutralising ADA response, which resulted in lower exposure, failure to achieve adequate B-cell depletion, one infusion-related reaction, and moderate EULAR response but poor ACR response. This case was thoroughly investigated and the observed response was considered likely to be a conjunction of various factors (Sjogren´s syndrome and an FF FcγRIIIa genotype) that may have had a role in the immune and PD response.

Due to different study design, only results up to Week 24 can be compared between study 1.1 and 3.2 (Part 1). In study CT-P10 1.1 ADAs were detected earlier with CT-P10 and the incidence rate was similar at Week 24 (19%) to that of MabThera (20%). In study 3.2 (Part 1) ADAs were detected earlier and their incidence at Week 24 was higher with both reference products (28% and 23%) compared to CT-P10 (14%). Importantly, in study 3.2, the ADA incidences were the same after the first and second treatment course.

In addition, the potential impact of ADA presence on PK and efficacy, the primary PK endpoints (AUC0-last, AUC0-inf and/or Cmax), DAS28 score and ACR response were assessed by ADA positive and negative subset in Studies CT-P10 1.1 and CT-P10 3.2. With regards to PK, the analyses concluded that ADA presence resulted in the reduced drug exposure but this impact was similar between CT-P10 and the reference products, MabThera and/or Rituxan. For efficacy, there was no clear trend observed in change from baseline of DAS28 score and ACR response at Week 24 between ADA positive and negative subset with virtually no difference between CTP10 and the reference products groups.

In Study CT-P10 3.3, immunogenicity data in 140 AFL patients indicates very low ADA incidence compared to CT-P10 RA studies. The proportions of patients with positive results for ADA up to Core Cycle 4 at post treatment visits were similar between the 2 treatment groups: 3/70 (4.3%) patients and 2/70(2.9%) patients in the CT-P10 and Rituxan group, respectively. All the ADA positive patients had positive for NAb with the exception of one patient in CT-P10 group. Because of higher drug concentrations and immunosuppression, immunogenicity

results in study CT-P10 3.3 are not particularly helpful for the comparability exercise; nevertheless, ADA incidence was broadly comparable under CT-P10 and Rituxan.

In CT-P10 3.3 (Part 1), due to the limited number of patients with ADA positive results, PK similarity was evaluated only in the ADA negative subset and a trend of lower exposure in terms of AUCtau and Cmax,ss was detected in the ADA positive subset with similar extents between the CT-P10 and Rituxan groups.

The impact of ADAs on exposure to rituximab appeared similar with both products. Based on current analyses, ADAs did not seem to influence PD, efficacy or safety parameters in most patients.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

In general, the Applicant´s development program to demonstrate the similarity between CT-P10 and Mabthera with respect to the pharmacokinetic (PK) is considered adequate and was performed according to the guidance on biosimilars and the recommendations given in the CHMP Scientific Advice.

In general, the design to evaluate pharmacokinetic equivalence of CT-P10 and Mabthera primarily in patients with RA (CT-P10 1.1) is considered appropriate. The studied population is considered appropriate for an initial investigation of PK because it is homogeneous in terms of target amount (B-cells) and is in line with the CHMP Scientific Advice. In addition to the completed Phase 1 studies, data from the first analysis of the ongoing Phase 3 studies has submitted: CT-P10 3.2 in RA patients (including primary PK and efficacy assessments up to Week 24) and CT-P10 3.3 in AFL patients (including primary PK assessment up to Core Cycle 4 [12 weeks]). The study CT-P10 3.3 in AFL patients was submitted as a supportive study to cover an oncology indication in line with the CHMP Scientific Advice.

The analytical method is acceptable and its validation reasonable. An unexpected level (about 30%) of baseline samples was found to be above the LLOQ of 0.02 µg/mL. This was further investigated and may be due to the presence of pre-existing HAMAs. Although the Applicant's assumption was not formally confirmed by the detection of HAMAs in the positive baseline samples, the assay was modified for the Phase III studies by the addition of mouse IgG in order to bind HAMAs if present in the sample. The proportion of positive baseline samples was greatly reduced by this method, which indirectly indicates that HAMAs may be at least one of the interfering factors.

For study CT-P10 1.1, additional PK analysis was conducted using all concentration data available from all patients having been administered 2,000 mg of rituximab. The new PK analysis includes geometric LS (least squares) means, ratios and 90% CI of the primary PK endpoints (C_{max} after the 2nd infusion and $AUC_{0\text{-}last}$) along with additional key PK parameters, i.e. $AUC_{0\text{-}t}$, $AUC_{t\text{-}inf}$, C_{max} after the 1st infusion and C_{trough} after the 1st infusion. This analysis showed that the 90%CIs of all the PK parameters were within the acceptance limits with ratios close to 100, therefore, these results fully support biosimilarity. This is further supported by consistent and similar results from Part 1 (up to Week 24) of Study CT-P10 3.2 in RA patients and PK similarity demonstrated from Part 1 (up to Core Cycle 4 [12 weeks]) in Study CT-P10 3.3 in AFL patients.

In Study CT-P10 3.2, all PK analyses were conducted using data from all patients who were administered 2,000 mg of rituximab. The comparative analysis of interest, CT-P10 vs. Mabthera, showed that, for all but one secondary parameter, all PK parameters were within the acceptance limits. The only parameter that had a 90%CI outside the limits (79.85 - 101.76) was $AUC_{t\text{-}inf}$. – and for this single parameter also, Mabthera was not equivalent to Rituxan- and as the 90%CI included 100% and the deviation was minor, this is considered

acceptable. However, most parameters indicated significantly lower exposure with CT-P10 compared to Mabthera; compared to the results of the previous trial, the ratios were lower (close to 90%). Of note, exposure to rituximab tended to be higher with Mabthera compared to Rituxan. The lower exposure observed with the commercial product CT-P10 compared to MabThera in study CT-P10 3.2 and the higher protein content of the MabThera product compared to the CT-P10 product used in the PK trial is a plausible explanation for the slightly higher exposure to rituximab in the MabThera arm. A thorough investigation was performed in order to elucidate the cause for the cases of higher than expected serum concentrations at week 24 in patients including assay-related factors and subject related factors. It was postulated that it may be due to the inherent variability associated with systemic rituximab concentrations. Furthermore sensitivity analysis suggested no impact on the bioequivalence or efficacy responses.

Additionally, other secondary PK parameters were also analysed in Study CT-P10 3.2 and the findings from these analyses are consistent between two RA studies and supports similarity between the two groups.

Study CT-P10 3.3 compared the final product to be marketed with Rituxan in patients with advanced follicular lymphoma (AFL) in both, PK population and ADA negative subset. Similarity of these products was demonstrated in this cancer patient population since the 90% CIs of geometric LS means ratio (CT-P10 to Rituxan treatment group) for AUC_{tau} and $C_{max,ss}$ were entirely contained in the equivalence range of 80% to 125% regardless of including or excluding outliers, which indicates that rituximab exposures from CT-P10 are similar to those from Rituxan. Due to the limited number of patients with ADA positive results, PK similarity was evaluated only in the ADA negative subset and a trend of lower exposure in terms of AUC_{tau} and $C_{max,ss}$ was detected in the ADA positive subset with similar extents between the CT-P10 and Rituxan groups.

There were no clinical differences observed between CT-P10 and Mabthera in FF genotype patients versus VF plus VV genotype patients, although a trend to lower AUCs for VF plus VV groups compared to the FF groups was observed; even though results in these subgroups remain within the standard margin of 80-125%.

The impact of immunogenicity on primary and secondary PK parameters, patients in PK population who did not show ADA was assessed separately. Furthermore, for the primary PK parameters, patients in PK population with positive ADA were assessed as a post-hoc base. Based on the data submitted for the primary PK parameters, similarity between CT-P10 and Mabthera was concluded for the PK (Antibody-negative subset), although in the PK (Antibody-positive subset), a difference is observed driven by fragmented power consequential to a small subset of antibody-positive patients across studies and high variability in individual PK and ADA titre values. Comprehensive analyses of the impact of ADA presence on PK and efficacy on assessing the extent of clinical relevance of such impact were carried out. These analyses were carried out not only in Study CT-P10 1.1 but also in the pivotal PK and therapeutic equivalence RA study, Study CT-P10 3.2. The analyses concluded that ADA presence resulted in reduced drug exposure but this impact was similar between CT-P10, Mabthera and Rituxan. In addition, this is a common observation and similarly with other approved biosimilar products, PK bioequivalence was not intended in the subgroup of antibody-positive patients (e.g., CT-P13, Remsima™/Inflectra™ in PK study in ankylosing spondylitis patients, where the 90% CIs of ratios of geometric means was outside of 80-125% for AUC_t in PK (antibody-positive subset) population (Remsima™ EPAR).

In conclusion, biosimilarity in terms of PK profiles for CT-P10 and Mabthera is demonstrated and supported by additional PK analyses for study CT-P10 1.1, PK analyses from Study CT-P10 3.2 which compared CT-P10, Mabthera and Rituxan and Study CT-P10 3.3 which compared CT-P10 and Rituxan.

Pharmacodynamics

B-cell depletion and recovery are considered clinically relevant markers of the therapeutic activity of rituximab. In accordance, B-cell counts have been selected as the key PD endpoint for the assessment of PD similarity between CT-P10 and Mabthera.

Having said that, there is no strong correlation between the extent of B-cell reduction (at least when using a B-cell assay that is not sufficiently sensitive) and the extent of the clinical response in RA. For NHL, the correlation is even less clear, since circulating B-cells may not directly reflect tumour mass, and this response cannot be considered as an appropriate surrogate of the clinical response.

In study CT-P10 1.1. mean B-cell levels BLOQ (20 cells/µl) were reached at the end of infusion in the CT-P10 arm. All patients but one in the Mabthera arm had reached levels below 20 cells/µl within 15 minutes after infusion end. In both study arms B-cell counts consistently remained below 20 cells/µl until week 16 for the majority of patients.

B-cell recovery is likely to be the most sensitive PD endpoint available. Available data from Study CT-P10 1.1, i.e., the conjunction of earlier re-treatment (58% in the CT-P10 arm vs. 45% in the MabThera arm) and earlier B-cell recovery in the remaining patients of the CT-P10 arm, seemed highly suggestive of a relevant difference in the duration of action of the two products, which would not be favourable to CT-P10.

In contrast to study CT-P10 1.1, study CT-P10 3.2 involved systematic retreatment at week 24, except for safety reasons (which occurred in 4 patients; 1%). Due to this design, little additional information is available to assess the duration of B-cell response.

B-cell results of study 3.2, decreased to below the LLoQ (20 cells/µL) immediately after the 1st infusion for all patients , except 1 in CT-P10 group, and then remained below this level up to Week 24 in the majority of patients in all treatment groups.

Nevertheless, the analysis of Part 1 showed a trend for earlier B-cell recovery with CT-P10 compared to MabThera and Rituxan. While the proportion of patients with B-cell recovery before week 48 was higher with Rituxan (31%) than CT-P10 (22%), it occurred in the majority of the cases at week 24 with Rituxan and at earlier time points with CT-P10. The proportion of patients with B-cell recovery was the lowest with MabThera (17%). When Parts 1 and 2 were combined, a slight difference between the two groups (CT-P10 and reference products) was apparent after the first treatment course. After the second treatment course, early B-cell recovery was infrequent regardless of the product.

Additional PD and efficacy analyses for both RA trials, including a time to event Kaplan-Meier analysis with the event being first B-cell value above LLoQ or discontinuation for lack of efficacy, suggest a trend for earlier B-cell recovery in CT-P10 arms and thus shorter duration of action that could need more frequent administrations. Unfortunately, the design of the pivotal RA efficacy trial involving systematic re-treatment at Week 24 cannot address this question.

In study C-P10 3. 3, in AFL population the extent of B-cell depletion appears similar between treatment arms, however updated data is still expected post-authorisation.

In RA, the durability of the clinical response to rituximab is known to be variable and unpredictable in different patients. Systematic re-treatment after 6 months is not recommended in the EU SmPC of MabThera but rather based on return of disease activity in order to avoid overtreatment and decrease infection risks.

The initial observation of Study 1.1 regarding the duration of activity of CT-P10 is likely a chance finding for the following reasons:

- Comparability of CT-P10 and MabThera has been demonstrated at the analytical and functional levels, with no differences suggesting different effects on B-cells.

- The method used to count B-cells in blood samples lacked sensitivity (BLQ of 20 cells/µL). It is noteworthy that highly sensitive flow cytometry can currently detect levels as low as 0.1 cells/µL and may allow to correlate B-cell depletion with clinical response.
- The trial was small and only numerical trends were observed (no statistical evidence), especially since individual responses are known to be very variable.

Therefore, biosimilarity of CT-P10 and MabThera from a PD perspective is considered demonstrated.

Uncertainties regarding the earlier ADA formation with CT-P10 compared to Mabthera have been addressed with as Study 3.2 showed opposite trend compared to those of Study 1.1. Moreover, the immunogenicity of the commercial CT-P10 product, which appeared lower to that of MabThera in the pivotal study, could potentially be due to the lower proportion and size of higher molecular weight (HMW) species, which have been associated with increased immunogenicity in the literature.

2.3.5. Conclusions on clinical pharmacology

PK analyses from study CT-P10 1.1 demonstrate that the PK profiles are comparable. In addition, PK data in both RA and AFL patients support the extrapolation to all other indications covered by Mabthera. Differences in B-cell recovery were observed but did not translate into lower efficacy (See Clinical efficacy).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

N/A

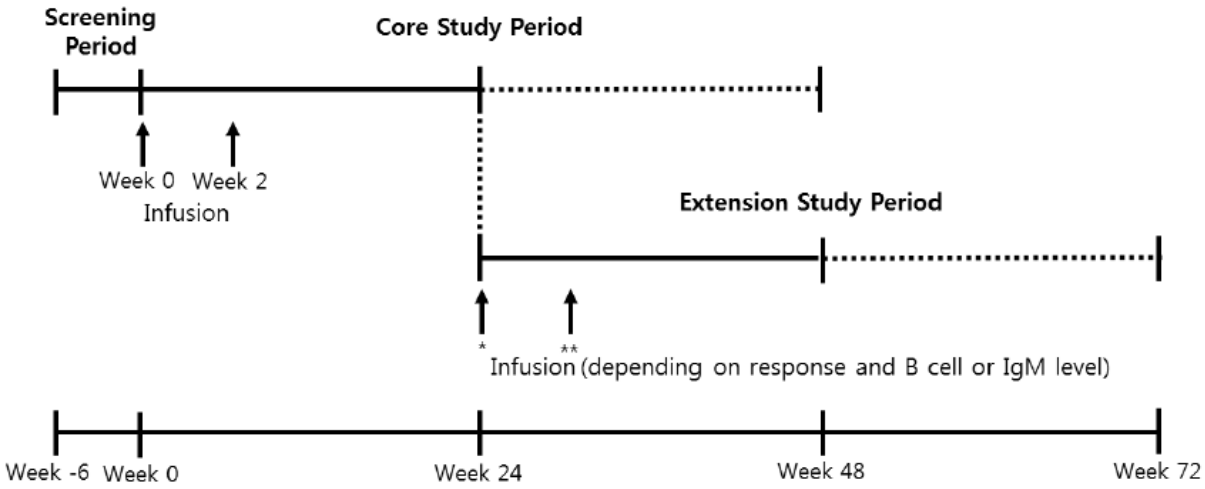
2.4.2. Main study

Study CT-P10 1.1: Phase 1, Randomized, Controlled, Multicenter, 2-Arm, Parallel-Group, Double-Blind Study to Demonstrate the Equivalence of CT-P10 to MabThera With Respect to the Pharmacokinetic Profile in Patients With Rheumatoid Arthritis

There were three periods in this study:

- *Screening Period*: from Week –6 through Week 0 (Day –42 to Day –1)
- *Core Study Period*: before initiation of the Extension Study Period, maximum up to 48 weeks
- *Extension Study Period* for eligible patients who received a second treatment course between 24 weeks and 48 weeks after the first infusion in the Core Study withy study duration of 24 weeks after the first infusion in the Extension Study Period

The total study duration was up to 72 weeks after the Week 0 infusion.



Methods

Study Participants

Main inclusion criteria

- male or female patients between 18 and 75 years old, inclusive
- diagnosed with RA according to the revised 1987 American College of Rheumatology (ACR) classification criteria for at least 6 months prior to randomization
- with active disease defined by the presence of 6 or more swollen joints and 6 or more tender joints, and serum C-reactive protein (CRP) ≥ 1.5 mg/dL or an erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour
- with previous MTX treatment (10 to 25 mg/week orally or parenterally) for at least the past 12 weeks, with the last 4 weeks at a stable dose, before Screening
- with inadequate response to previous or current treatment with the anti-TNF agents infliximab (≥3 mg/kg; at least 3 infusions for at least 3 months), golimumab (50 mg once a month for at least 12 to 14 weeks), adalimumab (40 mg every other week for at least 3 months), or etanercept (25 mg twice weekly or 50 mg once weekly for at least 3 months), or was intolerant to at least 1 administration of these agents.

Main exclusion criteria

- prior treatment with more than 2 biologic agents
- current or past history of chronic infection with hepatitis B, C or HIV
- recent history of severe infection or current diagnosis of tuberculosis (TB) or positive result for interferon-γ release assay (IGRA) with a negative examination of chest x-ray (patients with sufficient documentation of prophylaxis or complete resolution following TB treatment based on local guidelines could be enrolled)
- medical condition including uncontrolled diabetes mellitus or hypertension or cardiac disease, severe heart failure
- history of malignancy, organ transplantation, demyelinating disorders

Treatments

In the study CT-P10 1.1 patients were allowed to receive up to 2 courses of treatment. Each course consisted of 2 infusions of study drug (1,000 mg CT-P10 or Mabthera by IV infusion) with a 2 week interval between the first and second infusions. During the Core Study Period, study drug infusions were to occur on Week 0 and Week 2. If residual disease activity remained or if disease activity returned within 48 weeks from the first dose date in the Core Study Period, patients could be retreated with the second course of study drug (2 infusions) during the Extension Study Period, initiated between 24 weeks and 48 weeks after the first infusion in the Core Study Period based on the response evaluation result from Week 16 to Week 40.

CT-P10 and Mabthera were co-administered with MTX between 10 to 25 mg/week, orally or parenterally (dose and route had to be maintained from beginning to end of study) and folic acid ≥ 5 mg/week, oral dose.

Objectives

The primary objective of the study CT-P10 1.1 was to demonstrate similar PK in terms of area Under the serum Concentration-time curve from the start of the first infusion to the last measurable concentration after the second infusion (AUC0-last) and maximum serum concentration (Cmax) after the second infusion between CT-P10 and Mabthera in patients with active RA concomitantly treated with MTX and folic acid up to Week 24 of the Core Study Period.

The secondary objectives were to assess the additional PK variables of CT-P10 compared with Mabthera up to Week 24 of the Core Study Period and to evaluate the long-term efficacy, PD, overall safety and biomarkers of CT-P10 compared with Mabthera up to Week 72.

Outcomes/endpoints

PK parameters for rituximab were determined as primary endpoints (from the Core Study Period)

The main (secondary) efficacy endpoints were:

- ACR 20 % improvement criteria (ACR20), ACR 50 % improvement criteria (ACR50), and ACR 70 % improvement criteria (ACR70) at 8-week intervals
- Individual components of the ACR criteria compared to Baseline at 8-week intervals
    - Number of tender joints/swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling
    - Patient's assessment of pain using visual analogue scale (VAS)
    - Patient's and physician's global assessment of disease activity (VAS)
    - Health Assessment Questionnaire (HAQ) estimate of physical ability
    - CRP and ESR
    - Joint surgery
- Time to onset of ACR20 response
- Mean change from Baseline in disease activity measured by DAS28 (ESR) and DAS28 (CRP) at 8-week intervals
- Proportion of patients with a good response, defined according to EULAR response criteria at 8-week intervals
- CDAI and SDAI at 8-week intervals

Sample size

The study was powered to demonstrate PK equivalence of CT-P10 and MabThera in AUC0-last and Cmax. Equivalence was demonstrated if the 90% CI for the modeled ratio of CT-P10 to MabThera in AUC0-last and Cmax was within the bounds of 80% and 125%. Based on 90% power, a type I error of 0.1, an interpatient CV(%) in AUC0-last of 35%, and a true ratio of means of 1.0, 78 patients were needed in the CT-P10 treatment group and 39 patients were needed in the MabThera treatment group (117 patients in total). Allowing for a drop-out rate of 20%, 147 patients were to be randomly assigned into the study in a 2:1 allocation.

Randomisation

Patients were randomly assigned to treatment groups on Day 0 (before administration of study drug) by using a computer-generated randomization schedule prepared before the study. Patients were randomly assigned to a treatment group and assigned a kit schedule using an interactive web response system (IWRS) or interactive voice response system (IVRS). The randomization was stratified by region (European vs non-European) and prior anti-TNF-α blocker status (failure vs intolerant case).

During randomization, some patients were misrandomized with regard to their prior anti-TNF-α blocker status. A variable was derived called prior anti-TNF-α blocker status (modified), which was the patient's actual prior anti-TNF-α blocker status as recorded on the "Prior TNF Antagonist History" page of the eCRF. This variable was included in a sensitivity analysis of any model that used prior anti-TNF-α blocker status as a covariate.

Blinding (masking)

The unblinded randomization and materials kit schedules were developed by an independent team on a secure server and only distributed to named individuals (IVRS, packaging vendor, etc) as documented on a specification form signed by the sponsor. The study could be unblended only if specific emergency treatment were dictated by knowing the treatment status of the patient.

Statistical methods

The study was powered to demonstrate PK equivalence of CT-P10 and MabThera in AUC0-last and Cmax. Equivalence was demonstrated if the 90% CI for the modeled ratio of CT-P10 to MabThera in AUC0-last and Cmax was within the bounds of 80% and 125%

Seven patient populations were defined: all-randomized, PK, PK (antibody-negative subset), PK (antibody-positive subset), PD, efficacy, and safety. Patients who had any major protocol deviations might have been excluded from the PK, PD and/or efficacy population

The all-randomized population consisted of all patients enrolled and randomly assigned to receive a dose of either study drug (ie, allocated a randomization number as recorded on the "Randomization" eCRF), regardless of whether or not any study drug dosing was completed. Therefore, this population included all patients who were allocated a randomization number by IWRS/IVRS. Patients in the all-randomized population were analyzed according to the treatment to which they were randomly assigned. The all-randomized population was used as the denominator for percentages and data summaries were presented by randomized treatment.

Analysis for the Core Study Period visits was based on all patients in the all-randomized population. The efficacy population consisted of all patients who received at least 1 full dose of study drug (CT-P10 or MabThera) and provided at least 1 post-treatment efficacy result. Patients in the efficacy population were analyzed according to the treatment to which they were randomly assigned. This population was the primary analysis population for all

efficacy assessments. Analysis for the Core Study Period visits was based on all patients in the efficacy population.

Results

Participant flow

Study CT-P10 1.1

Table 10–1 Patient Disposition: All-Randomized Population

	CT-P10 1000 mg (N=103)	MabThera 1000 mg (N=51)	Total (N=154)
	Number (%) of patients		
Total number of patients			
Screened[a]	–	–	213
Randomized	103 (100.0)	51 (100.0)	154 (100.0)
Initiated Core Study Period	102 (99.0)	51 (100.0)	153 (99.4)
Completed Core Study Period	92 (89.3)	45 (88.2)	137 (89.0)
Primary reason for discontinuation (Core Study Period)			
Patient experienced no efficacy from study drug	2 (1.9)	1 (2.0)	3 (1.9)
Patient withdrew consent or the patient refused to continue treatment and/or procedures/observations	2 (1.9)	2 (3.9)	4 (2.6)
Patient had any adverse event that would compromise his/her safety if he/she continued to participate in the study	4 (3.9)	2 (3.9)	6 (3.9)
Significant or major protocol violation	1 (1.0)	0	1 (0.6)
Sponsor decision	1 (1.0)	1 (2.0)	2 (1.3)
Initiated Extension Study Period	60 (58.3)	23 (45.1)	83 (53.9)
Completed Extension Study Period	58 (56.3)	20 (39.2)	78 (50.6)
Primary reason for discontinuation (Extension Study Period)			
Patient withdrew consent or the patient refused to continue treatment and/or procedures/observations	1 (1.0)	0	1 (0.6)
Patient had any adverse event that would compromise his/her safety if he/she continued to participate in the study	1 (1.0)	2 (3.9)	3 (1.9)
Sponsor decision	0	1 (2.0)	1 (0.6)

[a] Includes screening failures and randomly assigned patients. If a patient was screened and randomly assigned, the treatment assigned was displayed in the "Randomized" row.

Recruitment

A total of 55 CT-P10 1.1 study centers were initiated in Europe, Asia, and Latin America. Of these study centers, 40 screened patients and 38 randomly assigned patients to treatment. On 07 March 2012 the first patient randomly was assigned to treatment; the last patient last visit took place on 4 February 2014.

Conduct of the study

The major protocol deviations reported in Study CT-P10 1.1 were noncompliance with inclusion and exclusion criteria (2 [1.9%] patients and 3 [5.9%] patients in the CT-P10 and MabThera treatment groups, respectively). Patients with major protocol deviations of noncompliance with inclusion and exclusion criteria were excluded from the PK, PD, and efficacy populations.

The original protocol (version 1.0), dated 29 June 2011, was amended 12 times during the course of the study. Of them, only 3 were global amendments. The most relevant changes were the following (all in the global amendment 4): the use of both prednisone and prednisolone was allowed; changed use of term “washout” to “discontinuation period” for consistency; clarified that the second course of therapy was to be decided upon a response evaluation result from Week 16 to Week 40; Any response evaluation result obtained after Week 40 (including an unscheduled visit) was not to be used to decide the second course of therapy.

Baseline data

- Baseline data

Table 2.7.3-7: Demographic Characteristics in Study CT-P10 1.1: All-Randomised Population

	CT-P10 1000 mg (N= 103)	MabThera® 1000 mg (N= 51)	Total (N= 154)
Age (years)			
Mean ± SD	49.8 ± 12.54	51.3 ± 10.86	50.3 ± 11.99
Median	52.0	53.0	52.0
Minimum, maximum	21, 75	23, 70	21, 75
Sex, n (%)			
Male	14 (13.6)	5 (9.8)	19 (12.3)
Female	89 (86.4)	46 (90.2)	135 (87.7)
Race, n (%)			

	CT-P10 1000 mg (N= 103)	MabThera® 1000 mg (N= 51)	Total (N= 154)
White	70 (68.0)	35 (68.6)	105 (68.2)
Black	0	0	0
Asian	15 (14.6)	9 (17.6)	24 (15.6)
Other	18 (17.5)	7 (13.7)	25 (16.2)
Not allowed by investigator country regulations	0	0	0
Height (cm)			
Mean ± SD	161.9 ± 8.03	162.1 ± 8.70	162.0 ± 8.23
Median	163.0	161.0	162.5
Minimum, maximum	144, 183	143, 183	143, 183
Weight (kg)			
Mean ± SD	71.23 ± 17.67	72.36 ± 15.97	71.61 ± 17.08
Median	68.00	71.70	69.25
Minimum, maximum	41.4, 135.3	43.5, 126.7	41.4, 135.3
Body mass index (kg/m^2)			
Mean ± SD	27.11 ± 6.04	27.53 ± 5.46	27.25 ± 5.84
Median	26.16	27.28	26.51
Minimum, maximum	17.5, 49.7	15.6, 46.5	15.6, 49.7
Region, n (%)			
European	61 (59.2)	30 (58.8)	91 (59.1)
Non-European	42 (40.8)	21 (41.2)	63 (40.9)
Number of Prior TNF-inhibitor, n (%)			
1	88 (85.4)	42 (82.4)	130 (84.4)
2	15 (14.6)	7 (13.7)	22 (14.3)
3	0 (0)	2 (3.9)	2 (1.3)
Prior anti-TNF-α inhibitor status, n (%)			
Failure	94 (91.3)	47 (92.2)	141 (91.6)
Intolerant Case	9 (8.7)	4 (7.8)	13 (8.4)
Duration for prior TNF-inhibitor use (month)			
Mean ± SD	19.07 ± 20.25	23.66 ± 26. 75	20.59 ± 22.63
Adalimumab	13.15 ± 13.78	22.06 ± 26.19	16.01 ± 18.91
Certolizumab	2.99 ± NC	3.02 ± NC	3.01 ± 0.02
Certolizumab pegol	31.03 ± 3.93	14.03 ± NC	25.36 ± 10.20
Etanercept	12.85 ± 9.31	20.57 ± 24.53	15.84 ± 17.10
Golimumab	24.63 ± 19.11	26.64 ± 31.45	25.03 ± 20.71
Infliximab	20.54 ± 27.05	16.28 ± 16. 42	18.99 ± 23.63
Investigational drug	13.39 ± 3.17	12.45 ± NC	13.16 ± 2.63

All patients took MTX and folic acid during the study, as per the study design and requirements. The mean ± SD dose of MTX taken during the study was similar between the 2 treatment groups (15.34 ± 4.82 mg/week and 15.59 ± 4.32 mg/week in the CT-P10 and Mabthera groups. All 153 (100.0%) patients had taken at least 1

anti-TNF-α blocker. The most frequently reported prior anti-TNF-α blockers were adalimumab, infliximab, and etanercept in both the CT-P10 and MabThera treatment groups

Overall, the duration of RA disease was similar between the 2 treatment groups. The mean ± SD time since RA diagnosis was 11.15 ± 7.91 years in the CT-P10 group and 10.26 ± 9.10 years in the Mabthera group. All patients had morning stiffness, arthritis of 3 or more joint areas, arthritis of hand joints, and symmetric arthritis at the time of diagnosis

Numbers analysed

Outcomes and estimation

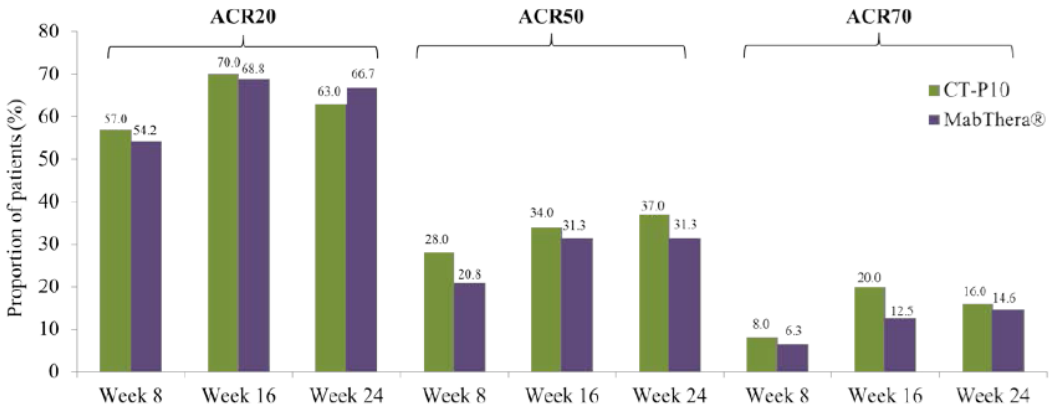
The proportion of patients achieving clinical response in the Core Study Period of CT-P10 1.1 according to the ACR20 criteria was similar in the CT-P10 and MabThera treatment groups.

Table 11–6 Proportions of Patients Achieving Clinical Response According to the ACR Criteria: Efficacy Population

Parameter	CT-P10 1000 mg (N=100)	MabThera 1000 mg (N=48)
Visit	n (%)	
ACR20		
Core Week 8	57 (57.0)	26 (54.2)
Core Week 16	70 (70.0)	33 (68.8)
Core Week 24	63 (63.0)	32 (66.7)
ACR50		
Core Week 8	28 (28.0)	10 (20.8)
Core Week 16	34 (34.0)	15 (31.3)
Core Week 24	37 (37.0)	15 (31.3)
ACR70		
Core Week 8	8 (8.0)	3 (6.3)
Core Week 16	20 (20.0)	6 (12.5)
Core Week 24	16 (16.0)	7 (14.6)

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

Note: For visits up to Core Week 24, percentages were calculated using the number of patients in the efficacy population as the denominator. The number of patients with the event was used as the numerator for all visits.



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

The 95 % CI for the difference of the change from baseline of DAS28 at Week 8, 16 and 24 was (-0.45, 0.37) and (-0.36, 0.43) at Week 8 for DAS28 (ESR) and DAS28 (CRP), (-0.34, 0.52) and (-0.32, 0.50) at Week 16, and (-0.39, 0.56) and (-0.36, 0.56) at Week 24, respectively.

Table 2.7.3-12: Analysis of DAS28 up to Week 24 in Study CT-P10 1.1: Efficacy Population

Visit/ Treatment Group	N'	Change from Baseline (Mean ± SD)	95% CI (Lower, Upper)	P-value
DAS28 (ESR)				
Core Week 8				
CT-P10	97	-1.73 ± 1.16	-0.45, 0.37	0.85
MabThera®	45	-1.69 ± 1.14		
Core Week 16				
CT-P10	96	-2.23 ± 1.24	-0.34, 0.52	0.69
MabThera®	45	-2.32 ± 1.11		
Core Week 24				
CT-P10	95	-2.07 ± 1.24	-0.39, 0.56	0.73
MabThera®	43	-2.15 ± 1.46		
DAS28 (CRP)				
Core Week 8				
CT-P10	97	-1.58 ± 1.10	-0.36, 0.43	0.86
MabThera®	44	-1.62 ± 1.07		
Core Week 16				
CT-P10	96	-2.06 ± 1.20	-0.32, 0.50	0.66
MabThera®	45	-2.15 ± 1.03		
Core Week 24				
CT-P10	95	-1.95 ± 1.16	-0.36, 0.56	0.66
MabThera®	43	-2.05 ± 1.45		

Note: Baseline is the last non-missing value on or before the Core Week 0 (D0) infusion.
CI: Confidence interval, CRP: C-reactive protein, DAS28: Disease Activity Score 28, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, N': Patient number who were analysed at each week.

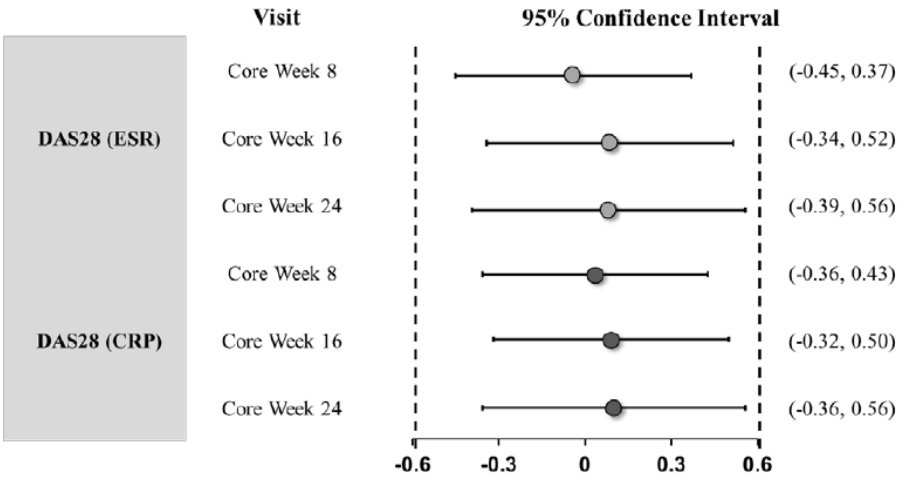


Figure 2.7.3-4: 95% CI Interval for Differences in Mean Change from Baseline of DAS28 in Study CT-P10 1.1: Efficacy Population

- Subgroups of interest

The efficacy of CT-P10 was evaluated in this subgroup of patients in with severe RA presenting with ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed), Study CT-P10 1.1 post-hoc analyses. The proportions of patients achieving ACR20 response in patients with ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed) was similar between CT-P10 and MabThera group at Week 8, 16 and 24. In addition, there were no significant differences observed compared to results including all patients

Table 2.7.3-24: Proportion of Patients Achieving Response According to ACR20 Criteria up to Week 24 in Patients with ≥ 8 Swollen Joints and Tender Joints in Study CT-P10 1.1: Efficacy Population

End Point	Time Point	Treatment Group	n/N (%)
ACR20	Core Week 8	CT-P10	54/91 (59.3 %)
		MabThera®	24/40 (60.0 %)
	Core Week 16	CT-P10	68/91 (74.7 %)
		MabThera®	30/40 (75.0 %)
	Core Week 24	CT-P10	60/91 (65.9 %)
		MabThera®	29/40 (72.5 %)

ACR20: ACR 20% improvement criteria

The changes from baseline values of DAS28 (ESR and CRP) at Week 8, 16 and 24 were also similar between CT-P10 and MabThera

Table 2.7.3-25: Baseline and Change from Baseline in Disease Activity Score by DAS28 in Patients with ≥ 8 Swollen Joints and Tender Joints in Study CT-P10 1.1: Efficacy Population

	CT-P10 1000 mg		MabThera® 1000 mg	
	N	Mean ± SD	N	Mean ± SD
Disease activity: DAS28 (ESR)				
Baseline	91	6.92 ± 0.76	40	6.87 ± 0.79
Core Week 8	88	-1.82 ± 1.16	39	-1.79 ± 1.16
Core Week 16	87	-2.34 ± 1.20	39	-2.44 ± 1.11
Core Week 24	86	-2.13 ± 1.26	38	-2.24 ± 1.49
Disease activity: DAS28 (CRP)				
Baseline	91	6.13 ± 0.79	40	6.14 ± 0.73
Core Week 8	88	-1.68 ± 1.09	39	-1.75 ± 1.03
Core Week 16	87	-2.18 ± 1.15	39	-2.29 ± 0.98
Core Week 24	86	-2.02 ± 1.18	38	-2.18 ± 1.44

CRP: C-reactive protein, DAS28: Disease activity score 28, ESR: Erythrocyte sedimentation rate, SD: Standard deviation

No clinically meaningful difference has been observed in results between Europe and non- European regions. Subgroup analysis using categorisation with Europe and non-Europe showed no relevant trends.

There are no clinical meaningful differences observed between CT-P10 and Mabthera groups in FF genotype patients, FV and VV genotype patients

Ancillary analyses

Historical Comparison between Study CT-P10 1.1 and MabThera studies

The mean ± SD change from baseline of DAS28 (ESR) was -2.3 ± 1.4 in Mabthera group in the REFLEX study and -2.4 ± 1.6 in the DANCER study, respectively. The results from Study CT-P10 1.1 showed consistency with those reported from the rituximab trials with changes from baseline values of -2.1 ± 1.3 and -2.2 ± 1.5 in CT-P10 and Mabthera groups at Week 24.

In CT-P10 Study 1.1, ACR20 at Week 24 were 65.9 % and 72.5 % in patients with ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed) in CT-P10 and Mabthera groups, respectively, which are slightly higher than that of the reported trials as in 51.3 % in REFLEX and 51.9 % in DANCER trials

Table 2.7.3-20: Comparison of Efficacy between Study CT-P10 1.1 and key MabThera® Studies with Similar Design

Efficacy Parameter		Historical Data		CT-P10 1.1 (Efficacy population)			
		Joint Count (Tender, Swollen) ≥ 8		Joint Count (Tender, Swollen) ≥ 6		Joint Count (Tender, Swollen) ≥ 8	
		REFLEX	DANCER	CT-P10	MabThera®	CT-P10	MabThera®
ACR20	Week 24 n/N (%)	153/298 (51.3 %)[2]	66/122 (54.1 %)[1] 96/185 (51.9 %)[2]	63/100 (63.0 %)	32/48 (66.7 %)	60/91 (65.9 %)	29/40 (72.5 %)
DAS28 (ESR)	Baseline Mean ± SD (n)	6.7 ± 1.0 (298)	6.7 ± NA (192)[2]	6.8 ± 0.8 (100)	6.7 ± 0.8 (47)	6.9 ± 0.8 (91)	6.9 ± 0.8 (40)
	Changes at Week 24 Mean ± SD (n)	-2.3 ± 1.4 (246)	-2.4 ± 1.6 (108)[3]	-2.1 ± 1.2 (95)	-2.1 ± 1.5 (43)	-2.1 ± 1.3 (86)	-2.2 ± 1.5 (38)
DAS28 (CRP)	Baseline Mean ± SD (n)	-	-	6.0 ± 0.9 (100)	6.0 ± 0.8 (47)	6.1 ± 0.8 (91)	6.1 ± 0.7 (40)
	Changes at Week 24 Mean ± SD (n)	-	-	-1.9 ± 1.2 (95)	-2.0 ± 1.5 (43)	-2.0 ± 1.2 (86)	-2.2 ± 1.4 (38)

[1]ITT RF-positive population, [2]ITT population, [3] ITT RF-positive population. Joint Only LOCF
ACR20: ACR 20% improvement criteria, CRP: C-reactive Protein, DAS28: Disease Activity Score 28, ESR: Erythrocyte sedimentation rate, LOCF: Last observation carried forward, NA: Not Available, SD: Standard deviation

In Study CT-P10 1.1, results of individual ACR components were similar between 2 treatment groups and the result was in line with results in the REFLEX trial with MabThera

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of efficacy for trial CT-P10 1.1

Title: a phase 1, randomised, controlled, multicentre, 2-Arm, parallel-group, double blind study to demonstrate the equivalence of CT-P10 to Mabthera with respect to the PK profile in patients with RA		
Study identifier	CT-P10 1.1	
Design	The study was designed to compare the PK, PD, efficacy and safety of CT-P10 and Mabthera reference product	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable Up to 48 weeks (total up to 72 weeks)
Hypothesis	Equivalence	
Treatments groups	CT-P10	CT-P10
	MabThera	MabThera

Endpoints and definitions	Primary endpoint	AUC0-last	Area under the serum concentration-time curve from the start of the first infusion to the last measurable concentration after the second infusion (covering data from 2 infusions combined
	Primary endpoint	Cmax	Maximum serum concentration after the second infusion
	Secondary endpoint	ACR20	ACR 20% improvement criteria (ACR20) at Week 24
	Secondary endpoint	DAS28	Mean change from Baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (ESR) and DAS28 (CRP) at 8-week intervals
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol At Week 24			
Descriptive statistics and estimate variability	Treatment group	CT-P10	MabThera	
	Number of subjects	96	45	
	AUC0-last (day*µg/mL) Geometric mean	7859.29	8110.54	
	Cmax (µg/mL) Geometric mean	465.76	486.32	
	DAS28 (ESR) Mean change from baseline SD	 -2.07 1.24	 -2.15 1.46	
	DAS28 (CRP) Mean change from baseline SD	 -1.95 1.16	 -2.05 1.44	

Effect estimate per comparison	Primary endpoint AUC0-last	Comparison groups	CT-P10 vs MabThera
		Geometric mean ratio (%)	96.90
		90% CI	88.10 – 106.58
	Primary endpoint Cmax	Comparison groups	CT-P10 vs MabThera
		Geometric mean ratio (%)	95.77
		90% CI	89.40 – 102.60
	Secondary endpoint DAS28 (ESR)	Comparison groups	CT-P10 vs MabThera
		Difference in mean from BL	0.08
		95%CI	-0.39 - 0.56
	DAS 28 (CRP)	95%CI	-0.36 - 0.56

Notes	

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive studies

Maintenance Study CT-P10 1.3

An Open-Label, Single-Arm, Maintenance Study to Demonstrate Long-Term Efficacy and Safety of CT-P10 in Patients with Rheumatoid Arthritis Who Were Treated with Rituximab (MabThera or CT-P10) in Study CT-P10 1.1

Location
The trial was conducted in 23 centres out of the 40 centres that participated in the Main Study and enrolled 87 patients.

Period
First subject first visit: 09-05-2013
Last patient last visit: 15-10-2014

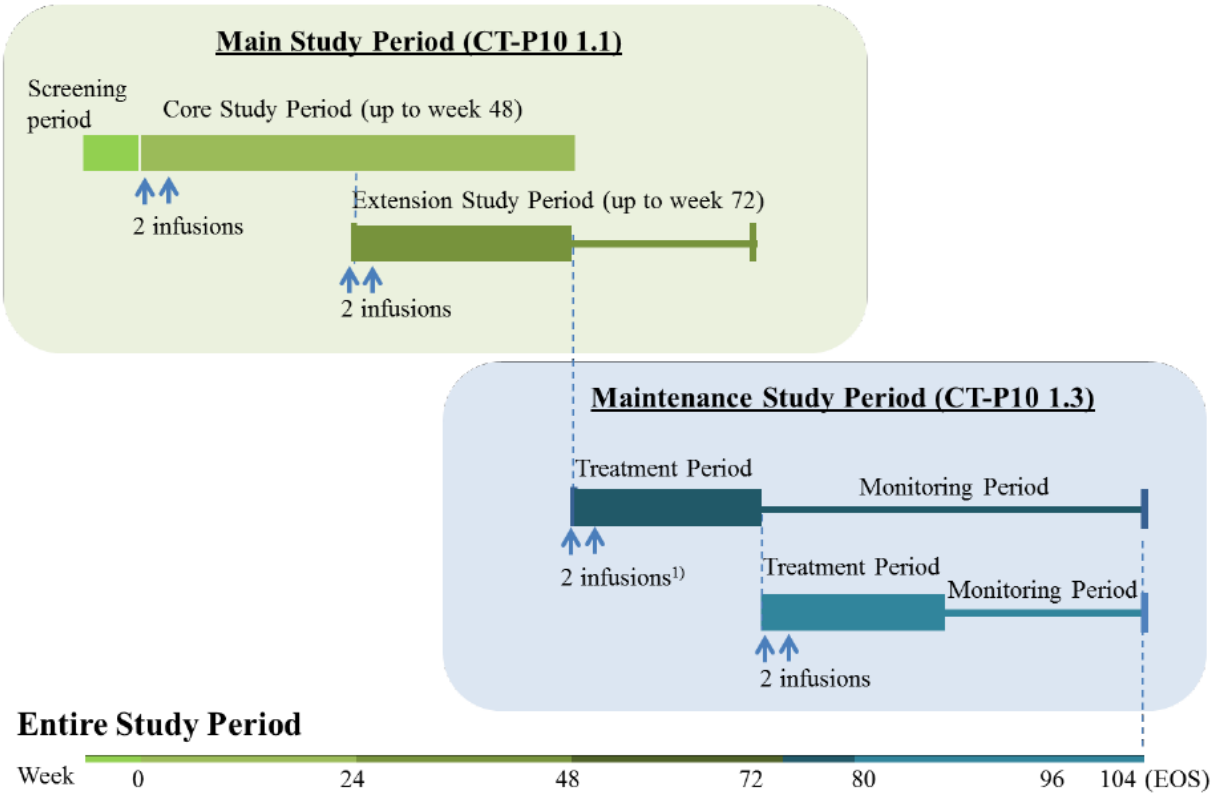
Methods

This was an open-label, single-arm, multicentre, efficacy and safety maintenance study of Study CT-P10 1.1. After the last visit of the Core Study Period (Week 48 of the Entire Study Period) or the last visit of the Extension Study Period (Week 24 of the Extension Study Period; up to Week 72 of the Entire Study Period) in Study CT-P10 1.1, eligible patients had the opportunity to continue in Study CT-P10 1.3 for a maximum of 56 weeks.

There were 3 periods in this study:

- Screening Period: Week –8 to Week 0 (Day –56 to Day –1)
- Monitoring Period: Every 8 weeks (±14 days) until the End-of-Study (EOS) Visit (after Week 96 and until Week 104 of the Entire Study Period) of the Maintenance Study Period (excluding the Treatment Period)
- Treatment Period: to be initiated between Week 48 and Week 80 of the Entire Study Period

The study duration up to the end of the study including the Screening Period was up to 64 weeks. The total duration of the Entire Study (Main Study and Maintenance Study) was up to 104 weeks.



Patients were eligible for CT-P10 infusion in the Maintenance Study if all the following criteria were met:

- They were responders to the previous course of treatment.
- Their disease activity returned during the Monitoring Period compared with the best response obtained between Weeks 16 and 24 from when their last treatment was initiated.
- Their B-cell or IgM levels were equal to or higher than the LLN or at least 50 % of the Main Study Period baseline level (Week 0 [Day 0] in Study CT-P10 1.1) using the results from previous visits.

Efficacy was evaluated using the same outcomes as in the Main Study.

The Efficacy Population consisted of all patients receiving at least 1 full dose of CT-P10 in this study and providing at least 1 post-treatment efficacy result. The baseline value was derived from the baseline value in Study CT-P10 1.1.

Patient disposition

A total of 87 patients initiated the Maintenance Study: 58 patients and 29 patients in the maintenance and switch treatment arms, respectively.

A similar proportion of patients in each treatment arm received a treatment course of CT-P10: 38 (65.5%) and 20 (69.0%), respectively. A single patient (from the maintenance arm) received a second treatment course.

Table 21 Patient disposition in the Maintenance Study

	Randomized Treatment from Study CT-P10 1.1		
	CT-P10 1000 mg (N=58)	MabThera 1000 mg (N=29)	Total (N=87)
	Number (%) of patients		
Total number of patients			
Initiated Maintenance Study Period	58 (100.0)	29 (100.0)	87 (100.0)
Completed Maintenance Study Period	47 (81.0)	21 (72.4)	68 (78.2)
Discontinued Maintenance Study Period	11 (19.0)	8 (27.6)	19 (21.8)
Discontinued Maintenance Study Period, prior to treatment start	8 (13.8)	5 (17.2)	13 (14.9)
Initiated first treatment period	38 (65.5)	20 (69.0)	58 (66.7)
Initiated second treatment period	1 (1.7)	0	1 (1.1)
Completed Maintenance Study Period who initiated any treatment in the Maintenance Study Period	35 (60.3)	17 (58.6)	52 (89.7)
Primary reason for discontinuation during Maintenance Study Period, prior to treatment start			
Patient developed sign of disease progression	0	1 (3.4)	1 (1.1)
Patient experienced no efficacy from study drug	1 (1.7)	0	1 (1.1)
Patient withdrew consent or the patient refused to continue treatment and/or procedures/observations	3 (5.2)	1 (3.4)	4 (4.6)
Patient developed, during the course of the study, symptoms or conditions listed in the exclusion criteria	1 (1.7)	0	1 (1.1)
Investigator decision	2 (3.4)	2 (6.9)	4 (4.6)
Other	1 (1.7)	1 (3.4)	2 (2.3)
Primary reason for discontinuation during Maintenance Study Period, after treatment start			
Patient developed sign of disease progression	1 (1.7)	0	1 (1.1)
Patient withdrew consent or the patient refused to continue treatment and/or procedures/observations	1 (1.7)	2 (6.9)	3 (3.4)
Other	1 (1.7)	1 (3.4)	2 (2.3)

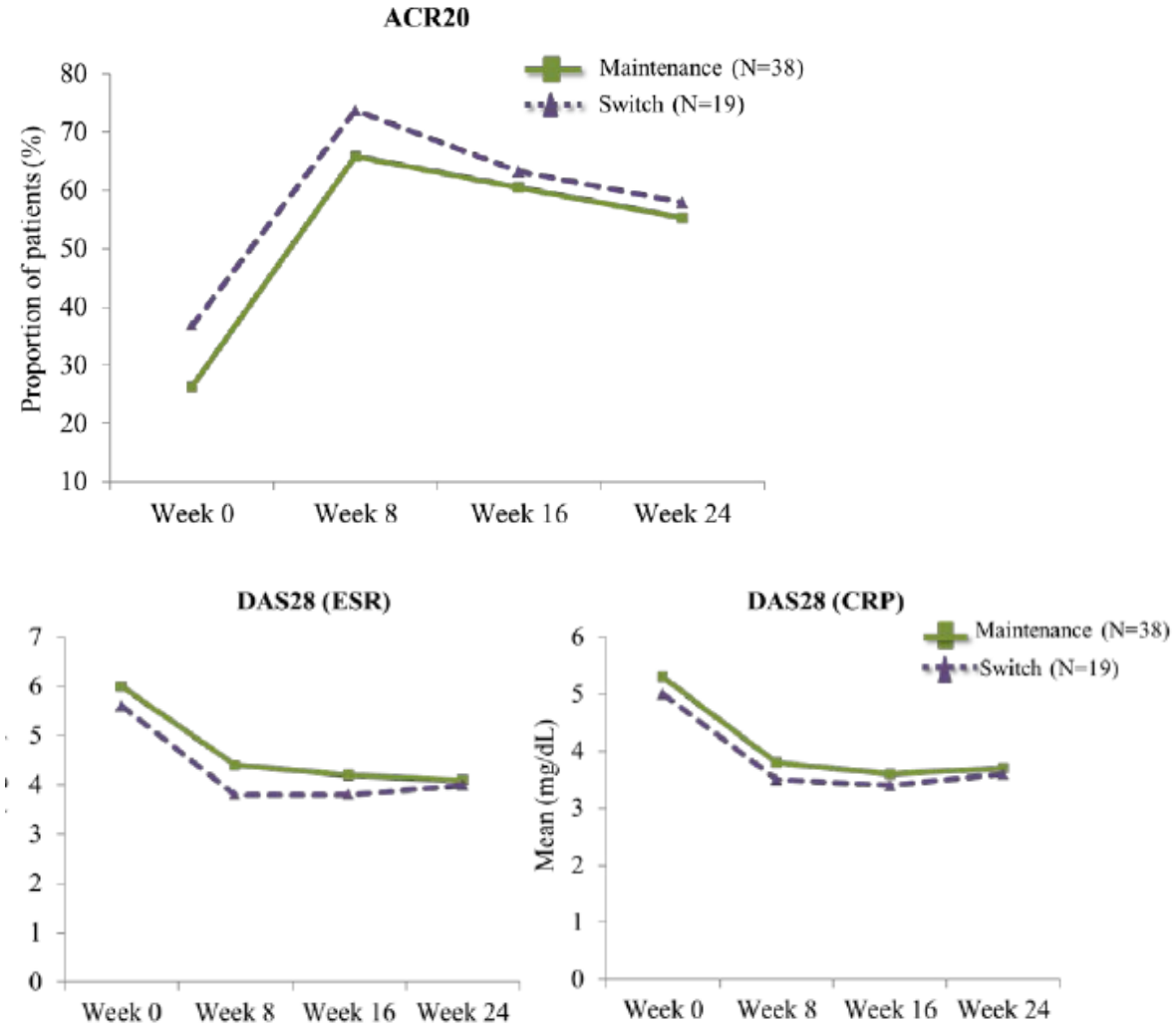
Outcomes

DAS28 and ACR20 results after an additional CT-P10 treatment course in the Maintenance Study are presented in Table 29 and Figure 5.

Table 27 Summary of DAS28 - Efficacy Population

Time point	DAS28 (ESR)		DAS28 (CRP)	
	CT-P10 Maintenance (N= 38)	CT-P10 Switch (N= 19)	CT-P10 Maintenance (N= 38)	CT-P10 Switch (N= 19)
	Mean ± SD			
Baseline	6.8 ± 0.83	6.5 ± 0.80	5.9 ± 0.90	5.8 ± 0.72
Treatment 1 Week 0	-0.8 ± 1.25	-0.9 ± 0.67	-0.6 ± 1.24	-0.8 ± 0.88
Treatment 1 Week 8	-2.4 ± 1.26	-2.6 ± 1.34	-2.1 ± 1.23	-2.3 ± 1.31
Treatment 1 Week 16	-2.6 ± 1.27	-2.7 ± 1.31	-2.3 ± 1.30	-2.4 ± 1.24
Treatment 1 Week 24	-2.7 ± 1.17	-2.4 ± 1.33	-2.2 ± 1.15	-2.2 ± 1.16

Figure 9 ACR20 response and mean DAS28 score- Efficacy Population



STUDY CT-P10 3.2

This study is a randomised, controlled, double-blind, parallel-group, Phase 3 study to compare the PK, efficacy and safety between CT-P10, Rituxan and Mabthera in Patients with rheumatoid arthritis (RA).

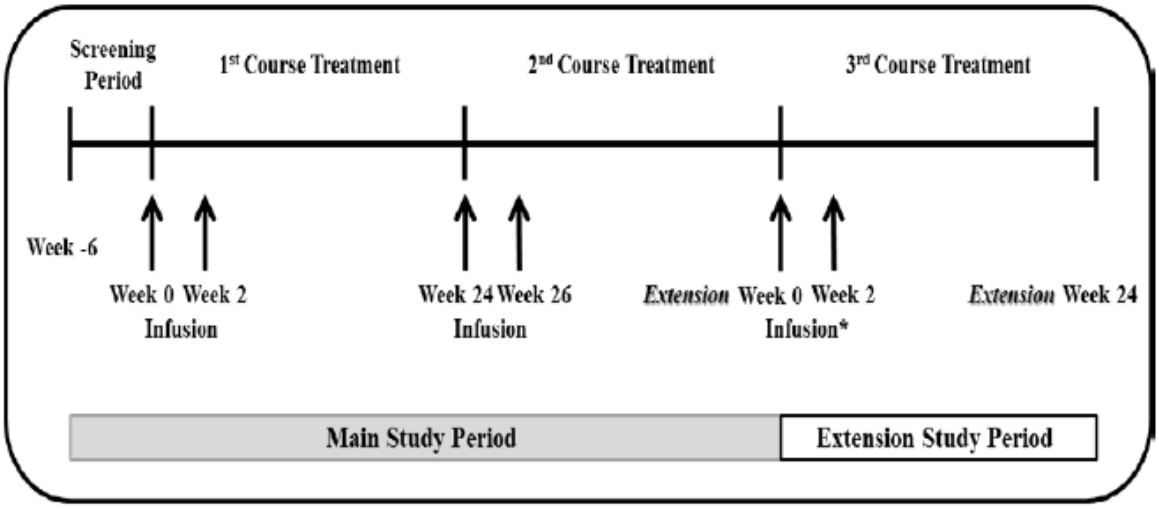
The overall objective of this study was to demonstrate similar pharmacokinetics and efficacy of CT-P10 compared to the reference products (Rituxan and Mabthera). With this purpose, this study was divided into 2 parts.

Part 1 was designed for demonstration of 3-way PK equivalence between CT-P10 and Mabthera, CT-P10 and Rituxan, Mabthera and Rituxan in terms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} (after the second infusion) of CT-P10 to Rituxan, CT-P10 to Mabthera, and Rituxan to Mabthera during the first treatment course (over the first 24 weeks).

Part 2 was intended to demonstrate therapeutic equivalence between CT-P10 and the combined reference products, Mabthera and Rituxan in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by DAS28 (CRP) at Week 24.

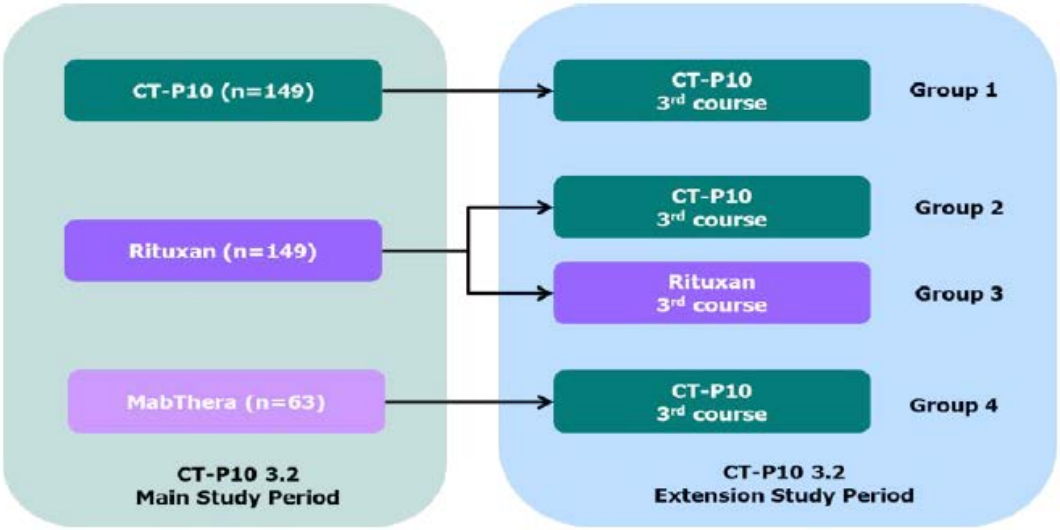
The Extension Study Period, which was designed to evaluate additional safety and immunogenicity, was initiated between Week 48 and Week 52 of the entire study period. The study duration was therefore up to 76 weeks after the Week 0 infusion.

Figure 9–1 Overall Study Schematic



* The third treatment course was initiated between Week 48 and Week 52 of the entire study period based on the results assessed within 8 weeks from Extension Week 0.

Figure 9–3 Patient Assignment for the Extension Study Period



A dose of 1,000 mg of CT-P10, Mabthera or Rituxan (IV) were co-administered with methotrexate (MTX) given at a dose between 7.5 to 25 mg orally or parenterally every week (dose and route had to be maintained from the beginning to the end of the study) and folic acid at a dose of ≥ 5 mg/week. Each course consists of 2 infusions separated by a 2-week interval. In the third treatment course (1 additional course in the Extension Study Period), patients who received Rituxan in the Main Study Period will be re-randomised to either the Rituxan or CT-P10 treatment groups and patients who received Mabthera in the Main Study Period will be switched to CT-P10 while patients who received CT-P10 will remain in CT-P10 group.

The main criteria for inclusion was male or female patients between 18 and 75 years old, inclusive, who had been diagnosed with rheumatoid arthritis according to the revised 1987 American College of Rheumatology (ACR) classification criteria for at least 6 months prior to randomization. Active disease was defined by the presence of 6 or more swollen joints and 6 or more tender joints, and serum CRP ≥1.5 mg/dL (≥15 mg/L) or an erythrocyte sedimentation rate (ESR) ≥28 mm/hour. Patients were to have received methotrexate treatment (7.5 to 25 mg/week orally or parenterally) for at least the past 12 weeks, with the last 4 weeks at a stable dose before screening. Patients were to have experienced an inadequate response to previous treatment with the anti-tumor necrosis factor (TNF) agents or were intolerant to these agents.

Therapeutic equivalence was concluded if the 95% CI for the treatment difference in the change from baseline of DAS28 (CRP) at Week 24 by the ANCOVA analysis was entirely within the equivalence margin of ±0.60. The least square means and associated 95% CI were reported by back transforming the least square means difference and 95% CI produced by these models.

A total of 372 male and female patients with RA were enrolled; 189 patients were included in Part 1 and 1:1:1 randomised into the CT-P10, Mabthera and the Rituxan group.

The analysis population used in this study is summarised in the following Table.

Population	CT-P10 (N=161)	MabThera® (N=60)	Rituxan® (N=151)	MabThera® + Rituxan® (N=211)	Total (N=372)
	Number (%) of patients				
Part 2					
All-Randomised	161 (100.0)	60 (100.0)	151 (100.0)	211 (100.0)	372 (100.0)
Safety	161 (100.0)	60 (100.0)	151 (100.0)	211 (100.0)	372 (100.0)
Safety - 2nd treatment course in Main Study Period Subset	142 (88.2)	58 (96.7)	138 (91.4)	196 (92.9)	338 (90.9)
Efficacy	155 (96.3)	59 (98.3)	144 (95.4)	203 (96.2)	358 (96.2)
Efficacy - 2nd treatment course in Main Study Period Subset	139 (86.3)	58 (96.7)	135 (89.4)	193 (91.5)	332 (89.2)
Pharmacodynamic	159 (98.8)	59 (98.3)	147 (97.4)	206 (97.6)	365 (98.1)
Pharmacodynamic - 2nd treatment course in Main Study Period Subset	142 (88.2)	58 (96.7)	137 (90.7)	195 (92.4)	337 (90.6)
Part 1					
All-randomized	64 (100.0)	60 (100.0)	65 (100.0)	125 (100.0)	189 (100.0)
Safety	64 (100.0)	60 (100.0)	65 (100.0)	125 (100.0)	189 (100.0)
Safety - 2nd treatment course in Main Study Period Subset	58 (90.6)	58 (96.7)	59 (90.8)	117 (93.6)	175 (92.6)
Efficacy	61 (95.3)	59 (98.3)	61 (93.8)	120 (96.0)	181 (95.8)
Efficacy - 2nd treatment course in Main Study Period Subset	57 (89.1)	58 (96.7)	57 (87.7)	115 (92.0)	172 (91.0)
Pharmacodynamic	62 (96.9)	59 (98.3)	62 (95.4)	121 (96.8)	183 (96.8)
Pharmacodynamic - 2nd treatment course in Main Study Period Subset	58 (90.6)	58 (96.7)	58 (89.2)	116 (92.8)	174 (92.1)

Note: Percentages are calculated by using the All-Randomized population as the denominator for the Part 1.

Patient disposition

	CT-P10 (N=161)	Rituxan (N=151)	MabThera (N=60)	Reference Products (N=211)	Total (N=372)
	Number (%) of patients				
Total number of patients					
- Screened	-	-	-	-	495
- Randomized	161	151	60	211	372
Initiated 1st treatment course	161 (100.0)	151 (100.0)	60 (100.0)	211 (100.0)	372 (100.0)
- Completed 1st treatment course	145 (90.1)	142 (94.0)	58 (96.7)	200 (94.8)	345 (92.7)
- Discontinued 1st treatment course	16 (9.9)	9 (6.0)	2 (3.3)	11 (5.2)	27 (7.3)
Primary reason for discontinuation (1st treatment course)					
- Patient experienced no efficacy from study drug	2 (1.2)	1 (0.7)	0	1 (0.5)	3 (0.8)
- Patient withdrew consent or patient refused	7 (4.3)	5 (3.3)	1 (1.7)	6 (2.8)	13 (3.5)
- Adverse event	2 (1.2)	3 (2.0)	1 (1.7)	4 (1.9)	6 (1.6)
- Significant or major protocol violation	2 (1.2)	0	0	0	2 (0.5)
- Lost to follow-up	1 (0.6)	0	0	0	1 (0.3)
- Patient died	1 (0.6)	0	0	0	1 (0.3)
- Investigator decision	1 (0.6)	0	0	0	1 (0.3)
Initiated 2nd treatment course	142 (88.2)	138 (91.4)	58 (96.7)	196 (92.9)	338 (90.9)
- Completed 2nd treatment course	140 (87.0)	134 (88.7)	56 (93.3)	190 (90.0)	330 (88.7)
– Discontinued 2nd treatment course	2 (1.2)	4 (2.6)	2 (3.3)	6 (2.8)	8 (2.2)
Primary reason for discontinuation (2nd treatment course)					
- Patient developed sign of disease progression	0	1 (0.7)	0	1 (0.5)	1 (0.3)
- Patient experienced no efficacy from study drug	0	1 (0.7)	1 (1.7)	2 (0.9)	2 (0.5)
- Patient withdrew consent or patient refuses	2 (1.2)	1 (0.7)	0	1 (0.5)	3 (0.8)
- Patient developed any malignancy	0	1 (0.7)	1 (1.7)	2 (0.9)	2 (0.5)
- Adverse event	0	1 (0.7)	0	1 (0.5)	1 (0.3)
- Lost to follow-up	1 (0.6)	1 (0.7)	0	1 (0.5)	2 (0.5)

Efficacy results

Demographic characteristics were similar among CT-P10, Mabthera, Rituxan and reference products groups.

Table: Demographic Characteristics in Study CT-P10 3.2: All-Randomised Population

	CT-P10 1000 mg	MabThera® 1000 mg	Rituxan® 1000 mg	MabThera® + Rituxan®	Total
Part 2					
Age (years)					
Mean ± SD	51.5 ± 11.54	50.8 ± 10.9	52.2 ± 11.3	51.8 ± 11.1	51.7 ± 11.3
Median	53.0	51.5	53.0	53.0	53.0
Minimum, maximum	18, 74	20, 74	21, 74	20, 74	18, 74
Gender, n (%)					
Male	23 (14.3)	10 (16.7)	21 (13.9)	31 (14.7)	54 (14.5)
Female	138 (85.7)	50 (83.3)	130 (86.1)	180 (85.3)	318 (85.5)
Race, n (%)					
White	91 (56.5)	41 (68.3)	97 (64.2)	138 (65.4)	229 (61.6)
Asian	12 (7.5)	5 (8.3)	7 (4.6)	12 (5.7)	24 (6.5)
Mestizo/Mestiza	47 (29.2)[1]	12 (20.0)	38 (25.2)	50 (23.7)	97 (26.1)
Hispanic	9 (5.6)	0	4 (2.7)	4 (1.9)	13 (3.5)
Mixed	2 (1.2)	2 (3.3)	5 (3.3)	7 (3,3)	9 (2.4)
Height (cm)					
Mean ± SD	162.1 ± 9.1	162.1 ± 7.6	162.6 ± 9.6	162.5 ± 9.1	162.3 ± 9.1
Median	162.0	162.5	162.0	162.0	162.0
Minimum, maximum	144, 188	145, 179	142, 194	142, 194	142, 194
Weight (kg)					
Mean ± SD	70.6 ± 17.1	69.8 ± 18.1	71.5 ± 16.4	71.0 ± 16.9	70.8 ± 17.0
Median	67.0	66.3	71.0	70.0	68.7
Minimum, maximum	38.0, 119.5	39.3, 139.0	40.0, 134.5	39.3, 139.0	38.0, 139.0
Body mass index (kg/m^2)					
Mean ± SD	26.8 ± 5.9	26.5 ± 6.1	27.0 ± 5.6	26.9 ± 5.7	26.8 ± 5.8
Median	25.7	25.7	26.0	26.0	25.9
Minimum, maximum	17.8, 52.8	15.4, 48.1	16.6, 55.0	15.4, 55.0	15.4, 55.0
Region, n (%)					
European Union[1]	38 (23.6)	21 (35.0)	44 (29.1)	65 (30.8)	103 (27.7)
Non-European Union[2]	123 (76.4)	39 (65.0)	107 (70.9)	146 (69.2)	269 (72.3)
Number of Prior TNF-inhibitor use, n (%)					
0	2 (1.2)	0	0	0	2 (0.5)
1	144 (89.4)	49 (81.7)	134 (88.7)	183 (86.7)	327 (87.9)
2	14 (8.7)	11 (18.3)	17 (11.3)	28 (13.3)	42 (11.3)
3	1 (0.6)	0	0	0	1 (0.3)
Prior anti-TNF-α inhibitor status, n (%)					
Inadequate response	138 (85.7)	55 (91.7)	132 (87.4)	187 (88.6)	325 (87.4)
Intolerant Case	21 (13.0)	5 (8.3)	19 (12.6)	24 (11.4)	45 (12.1)

All patients received MTX and folic acid during the study, as per the study design and requirements. The mean ± SD dose of MTX taken at the 1st infusion in Part 1 was similar among the 4 treatment groups (15.23 ± 4.93

in CT-P10 group, 15.63 ± 5.01 in Mabthera group. 15.46 ± 5.21 in Rituxan group and 15.54 ± 5.10 in reference products group, respectively). In Part 2, the mean ± SD dose of MTX taken at the 1st infusion was similar to Part 1 and was similar among the 4 treatment groups (14.61 ± 4.34 in CT-P10 group, 15.63 ± 5.01 in Mabthera group. 14.77 ± 4.51 in Rituxan group and 15.01 ± 4.66 in reference products group, respectively).

Overall, the duration of RA disease was similar among the treatment groups in Part 1 and Part 2. The mean ± SD time since RA diagnosis was 9.4 ± 6.8 years in the CT-P10 group, 9.9 ± 7.4 years in the Mabthera group, 8.2 ± 5.3 years in the Rituxan group and 9.0 ± 6.43 in reference products group in Part 1, respectively. The mean ± SD time since RA diagnosis in Part 2 was 10.7 ± 8.0 years in the CT-P10 group, 9.9 ± 7.4 years in the Mabthera group, 8.8 ± 7.4 years in the Rituxan group and 9.1 ± 7.4 in reference products group, respectively.

In the efficacy population, the change from baseline in disease activity measured by DAS28 (CRP) at Week 24 was compared using ANCOVA. In the efficacy population, the 95% CIs for the estimate of treatment difference was well within the pre-defined equivalence margin of 0.6 and hence, the therapeutic equivalence between CT-P10 and reference products group in terms of change from baseline in DAS28 (CRP) at Week 24 has been established at the 5% level of significance. A similar result was found in change from baseline of DAS28 (ESR), showing no significant difference between CT-P10 and reference products groups. The same analysis has been carried out in the all-randomised population as a sensitivity analysis.

Visit/ Treatment Group	N'	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
All-Randomised Population				
DAS28 (CRP)				
CT-P10	140	-2.13 (0.175)	-0.05	(-0.29, 0.20)
MabThera® + Rituxan®	197	-2.09 (0.176)		
DAS28 (ESR)				
CT-P10	141	-2.41 (0.181)	-0.06	(-0.31, 0.20)
MabThera® + Rituxan®	197	-2.36 (0.181)		
Efficacy Population				

Visit/ Treatment Group	N'	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
DAS28 (CRP)				
CT-P10	139	-2.14 (0.177)	-0.05	(-0.29, 0.20)
MabThera® + Rituxan®	196	-2.09 (0.176)		
DAS28 (ESR)				
CT-P10	140	-2.41 (0.182)	-0.06	(-0.31, 0.19)
MabThera® + Rituxan®	196	-2.35 (0.182)		

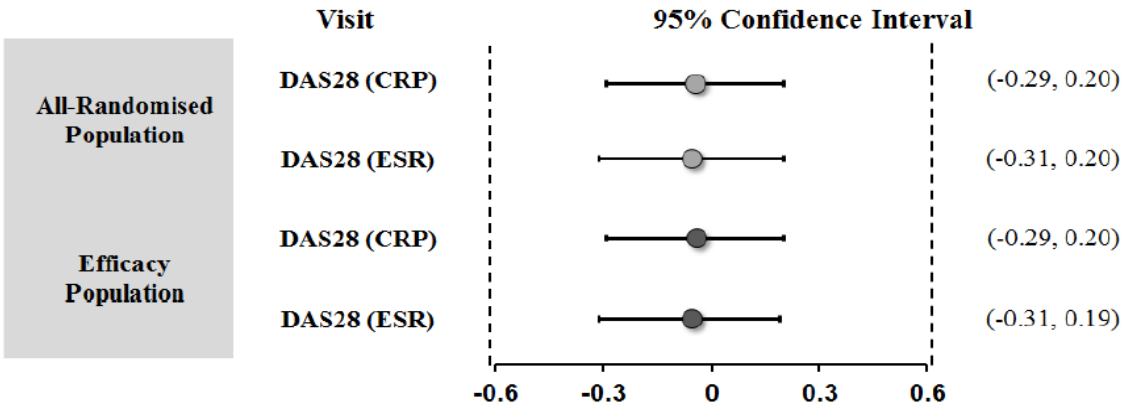


Table 22: Baseline Values and Change from Baseline in Disease Activity Measured by DAS28 at Weeks12 and 24 in Study CT-P103.2: Efficacy Population

	CT-P10 1000 mg (N=155)		MabThera® 1000 mg (N=59)		Rituxan® 1000 mg (N=144)		MabThera® + Rituxan® (N=203)	
	Mean ± SD							
Disease activity: DAS28 (CRP)								
Baseline	n=155	5.83 ± 0.91	n=59	5.99 ± 0.87	n=144	5.77 ± 0.92	n=203	5.83 ± 0.91
Week 12	n=140	-2.15 ± 0.94	n=59	-1.86 ± 1.07	n=140	-1.99 ±0.95	n=199	-1.95 ± 0.98
Week 24	n=139	-2.34 ± 1.06	n=58	-2.26 ± 1.30	n=138	-2.29 ± 1.11	n=196	-2.28 ± 1.17
Disease activity: DAS28 (ESR)								
Baseline	n=155	6.71 ± 0.83	n=59	6.77 ± 0.75	n=144	6.66 ± 0.84	n=203	6.70 ± 0.81
Week 12	n=143	-2.33 ± 0.99	n=59	-2.04 ± 1.22	n=141	-2.18 ± 0.91	n=200	-2.14 ± 1.01
Week 24	n=140	-2.55 ± 1.13	n=58	-2.35 ± 1.31	n=138	-2.52 ± 1.13	n=196	-2.47 ± 1.18
Number of tender joints								
Baseline	n=155	14.8 ± 6.36	n=59	15.0 ± 5.92	n=144	14.0 ± 6.20	n=203	14.3 ± 6.12
Week 12	n=143	-9.4 ± 5.23	n=59	-8.0 ± 6.50	n=141	-8.2 ± 4.98	n=200	-8.1 ± 5.45
Week 24	n=140	-9.7 ± 5.26	n=58	-8.7 ± 5.52	n=138	-9.2 ± 5.19	n=196	-9.0 ± 5.28
Number of swollen joints								
Baseline	n=155	11.4 ± 5.24	n=59	11.6 ± 5.17	n=144	11.1 ± 4.87	n=203	11.2 ± 4.95
Week 12	n=143	-8.3 ± 4.14	n=59	-6.7 ± 5.25	n=141	-7.9 ± 3.93	n=200	-7.6 ± 4.38
Week 24	n=140	-8.4 ± 4.40	n=58	-7.3 ± 4.42	n=138	-8.1 ± 4.54	n=196	-7.9 ± 4.51

CRP: C-reactive protein, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, SD: Standard deviation

Figure 10: Mean Score of DAS28 (CRP) and DAS28 (ESR) up to Week 24 in Study CT-P10 3.2: Efficacy Population

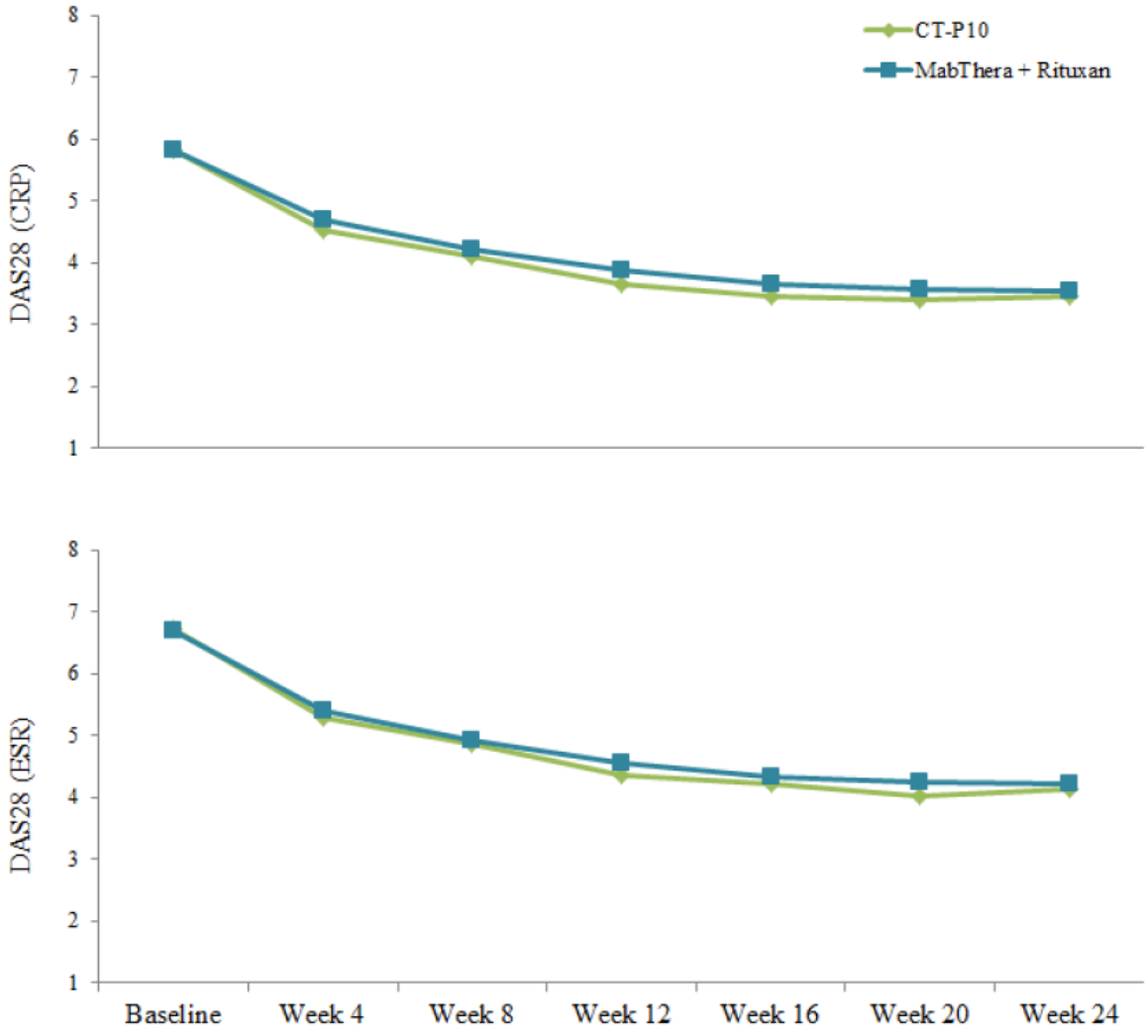
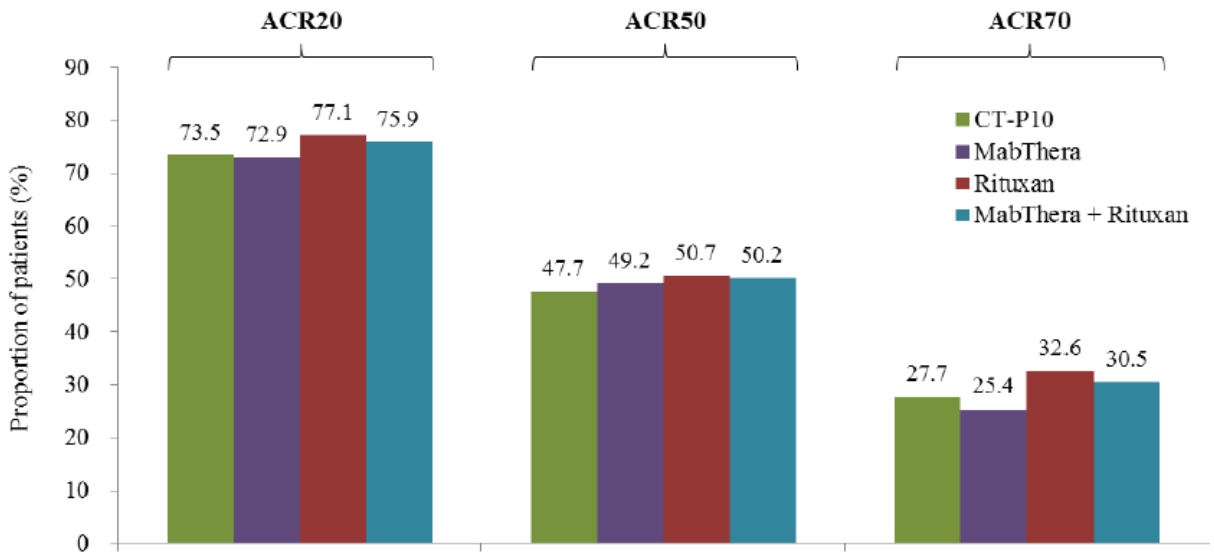
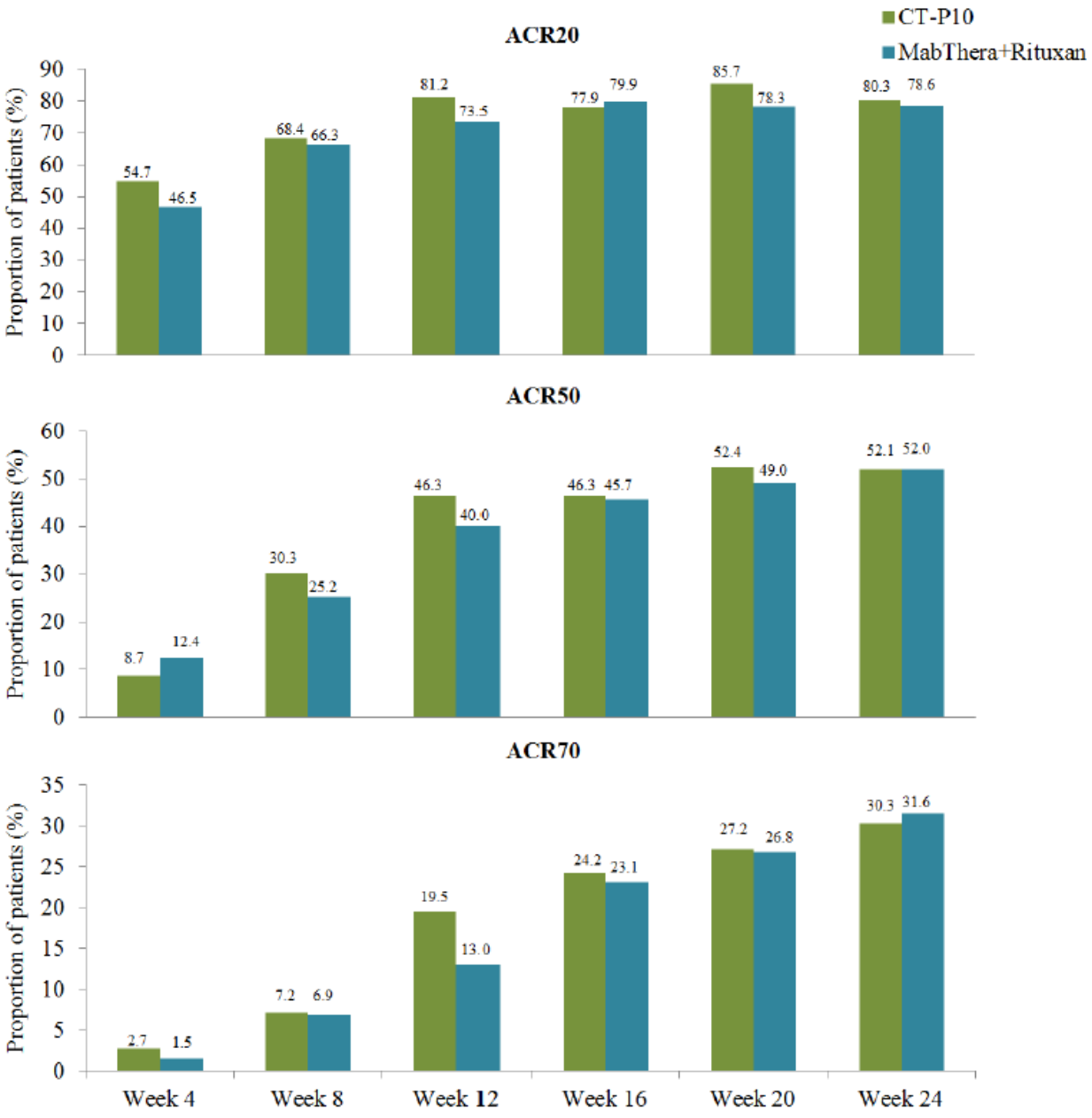


Table 23: Proportion of Patients Achieving Clinical Response according to the ACR Criteria in Study CT-P10 3.2: Efficacy Population

Parameter Visit	CT-P10 1000 mg (N = 155)	MabThera® 1000 mg (N = 59)	Rituxan® 1000 mg (N = 144)	MabThera® + Rituxan® (N = 203)
	Number (%) of Patients			
ACR20				
Week 24	114/155 (73.5)	43/59 (72.9)	111/144 (77.1)	154/203 (75.9)
ACR50				
Week 24	74/155 (47.7)	29/59 (49.2)	73/144 (50.7)	102/203 (50.2)
ACR70				
Week 24	43/155 (27.7)	15/59 (25.4)	47/144 (32.6)	62/203 (30.5)



In addition, the Applicant has performed an additional analysis for proportion of patients achieving clinical response according to ACR20/50/70 at 4-weeks interval as a post-hoc manner. The number of patients achieving ACR20/50/70 was similar between CT-P10 and reference products groups at earlier time points as well.



The sensitivity analysis for the proportions of patients achieving clinical responses according to ACR20, ACR50 and ACR70 criteria in Study CT-P10 3.2 were conducted with treating missing data as a non-responder. These analyses aligned with the initial results which were performed without missing data imputation

In the efficacy population, the mean decreases from baseline were similar among CT-P10, Mabthera, Rituxan and the reference products groups throughout the study for the following ACR components: mean number of tender joints, mean number of swollen joints, mean VAS scores for the patient assessment of pain, mean VAS scores for the patient and physician global assessment of disease activity, mean score for the HAQ estimate of physical ability, CRP and ESR.

The median (25th percentile, 75th percentile) time to onset of ACR20 response was shorter for patients in CT-P10 group than patients in Mabthera and Rituxan groups (median [25th percentile, 75th percentile] was 30.0 [29.0, 60.0] days in CT-P10 group, 57.0 [29.0, 85.0] days in Mabthera group and 56.0 [29.0, 85.0] days in Rituxan group, respectively), but this finding should be treated with caution due to limited evaluation time points. In addition, there was no statistically meaningful difference between CT-P10 and reference products groups when analysed using Log-rank test (p=0.4317).

The mean hybrid ACR scores at Week 24 were similar among CT-P10, Mabthera, Rituxan and the reference products groups (mean [SD] score were 51.68 [25.38] in CT-P10 group, 50.54 [27.34] in Mabthera group, 52.39 [24.56] in Rituxan group and 51.84 [25.35] in reference products group, respectively) in the efficacy population.

The mean decreases from baseline in SDAI and CDAI at each time point were similar between theCT-P10, Mabthera, Rituxan and reference products groups.

Visit	CT-P10 (N=155)	MabThera® (N=59)	Rituxan® (N=144)	MabThera® + Rituxan® (N=203)
	(Mean ± SD)			
SDAI				
Baseline	41.85 ± 13.00	43.84 ± 13.53	40.76 ± 12.88	41.65 ± 13.11
Week 24	-26.89 ± 11.31	-25.43 ± 12.71	-26.21 ± 11.45	-25.98 ± 11.81

Visit	CT-P10 (N=155)	MabThera® (N=59)	Rituxan® (N=144)	MabThera® + Rituxan® (N=203)
	(Mean ± SD)			
CDAI				
Baseline	39.58 ± 12.06	40.40 ± 11.70	38.41 ± 11.49	38.99 ± 11.56
Week 24	-25.57 ± 10.91	-23.27 ± 12.09	-24.96 ± 10.89	-24.46 ± 11.26

Note: Baseline is the last non-missing value on or before the 1st infusion
CDAI: Clinical disease activity index, SD: Standard deviation, SDAI: Simplified disease activity index

Long term data

Long-term efficacy data up to Week 48 in Study CT-P10 3.2 were also analysed.

The efficacy population was used as the main analysis set for efficacy. As a matter of sensitivity analyses, efficacy was analysed in ITT population.

For DAS28 analysis, the change from baseline in disease activity measured by DAS28 was analysed using an ANCOVA method which is as specified in the SAP. In the efficacy population, the 95% CIs for the estimate of

treatment difference for both DAS28 (CRP) and DAS28 (ESR) were well within ± 0.60 up to Week 48; ± 0.60 was the pre-specified therapeutic margin of Study CT-P10 3.2 for the primary endpoint at 24 weeks.

For DAS28 (CRP), the 95% CIs of the differences between the CT-P10 and reference product groups during the 1st treatment course were (-0.32, 0.07), (-0.33, 0.09), (-0.39, 0.03), (-0.36, 0.08), (-0.36, 0.13) and (-0.29, 0.20) at Weeks 4, 8, 12, 16, 20 and 24, respectively. For the 2nd treatment course over the longer term period, the 95% CIs of the differences were (-0.34, 0.16), (-0.35, 0.19) and (-0.35, 0.21) at Weeks 32, 40 and 48, respectively.

For DAS28 (ESR), the 95% CIs of the differences between the CT-P10 and reference product groups during the 1st treatment course were (-0.32, 0.08), (-0.29, 0.13), (-0.39, 0.04), (-0.30, 0.16), (-0.45, 0.05) and (-0.31, 0.19) at Weeks 4, 8, 12, 16, 20 and 24, separately. For the 2nd treatment course over the longer term period, the 95% CIs of the differences were (-0.41, 0.11), (-0.44, 0.13) and (-0.41, 0.20) at Weeks 32, 40 and 48, respectively.

Overall, the efficacy between the 2 treatment groups was maintained to a similar degree over the long-term period up to Week 48.

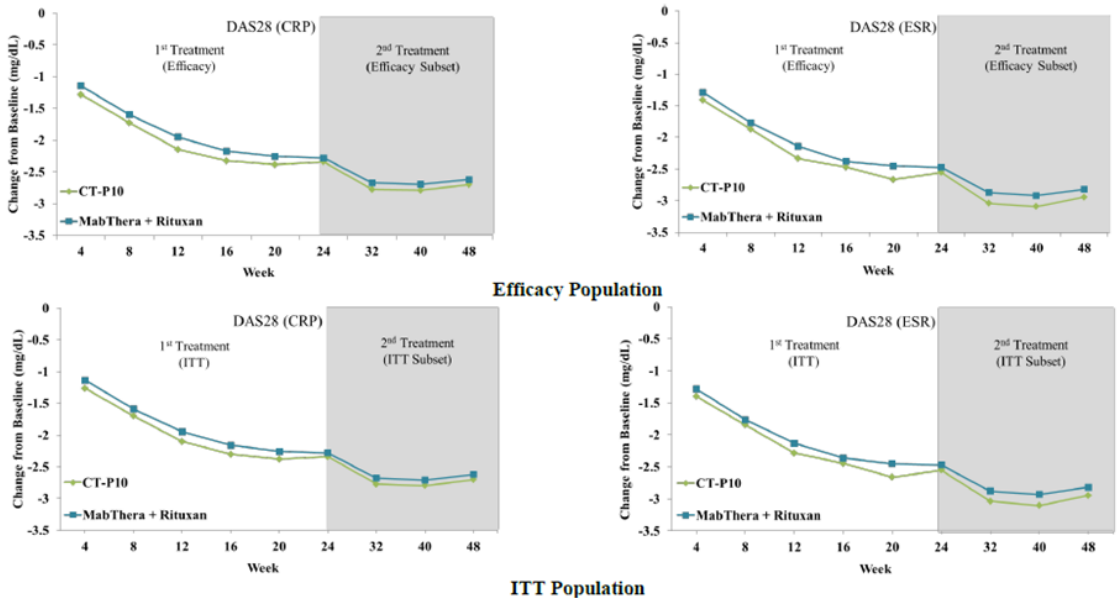


Figure 11: **Mean Change from Baseline of DAS28 (CRP, ESR) up to Week 48 in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset – Part 2**

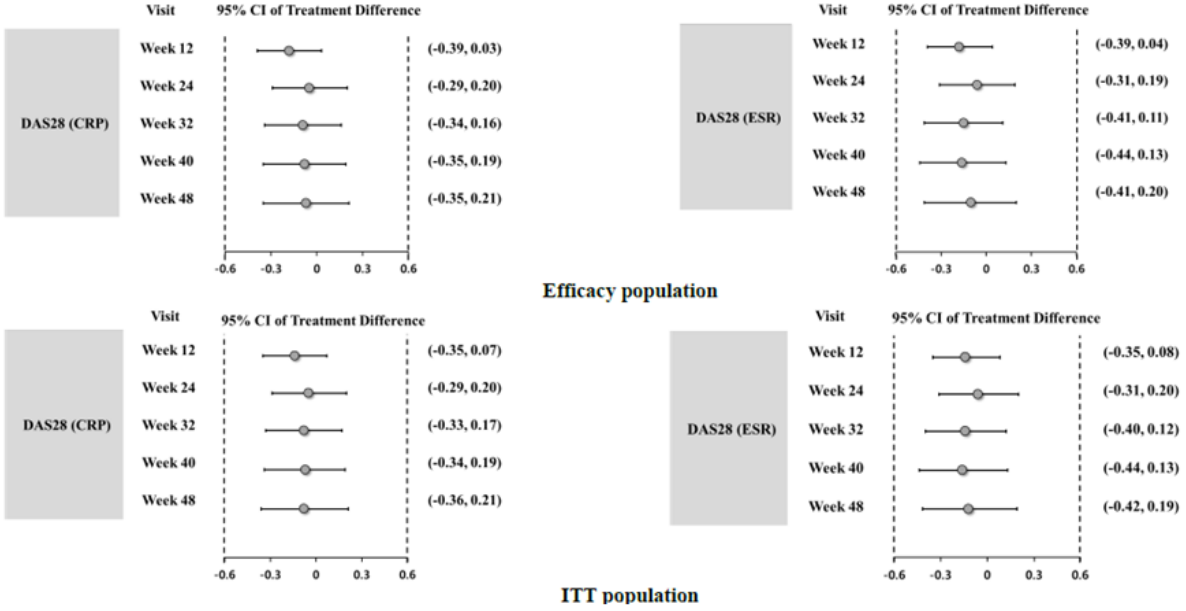


Figure 12: **ANCOVA Analysis (95% CI for Difference) in DAS28 (CRP, ESR) in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset – Part 2**

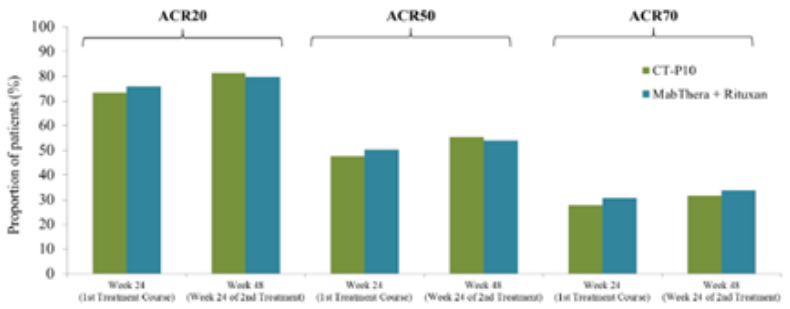
Long-term efficacy was also evaluated using ACR analyses.

In the efficacy population, the proportions of patients achieving clinical response according to the ACR20/50/70 were similar between the CT-P10 and the reference products groups up to Week 48. The proportions increased until Week 20 and were maintained in the long-term period over 48 week in the 2 treatment groups.

For ACR20, the 95% CIs of the differences between the CT-P10 and reference products groups during the 1st treatment course were (-0.04, 0.18), (-0.08, 0.12), (-0.02, 0.16), (-0.11, 0.06), (- 0.02, 0.15) and (-0.11, 0.07) at Weeks 4, 8, 12, 16, 20 and 24, respectively. For the 2nd treatment course over the longer term period, the 95% CIs of the differences were (-0.07, 0.07) (-0.06, 0.09) (-0.07, 0.10) at Weeks 32, 40 and 48,

respectively. The 95% CI of the differences according to the ACR50 and ACR70 criteria were also similar between the CT-P10 and reference products groups.

Overall, the efficacy between CT-P10 and reference products groups remained similar over the long-term period up to Week 48, which provides reassurance on the therapeutic equivalence derived from change from baseline in DAS28 (CRP) at Week 24.



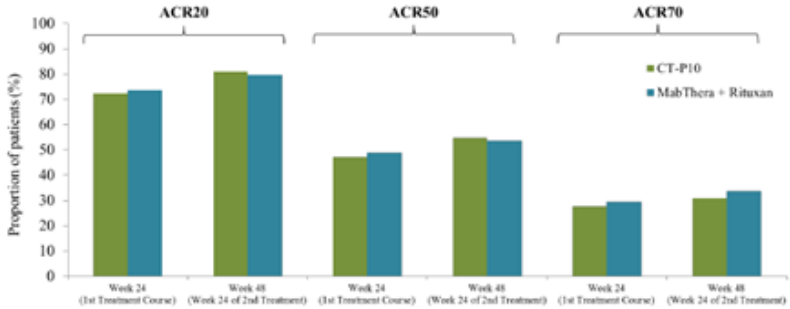


Figure 13: **Proportion of Patients Achieving Response according to ACR Criteria (ACR20/50/70) at Week 24 and 48 in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset (Logistic Regression) - Part 2**

- Long-term Efficacy Data in Part 1

Same efficacy analyses as conducted on the Part 2 patients were also executed for the Part 1 patients of Study CT-P10 3.2, where the patients were randomised in a 1:1:1 to receive CT-P10: Mabthera: Rituxan. This allows respective comparison of CT-P10 versus Mabthera and CT-P10 versus Rituxan to support in-depth comparison among 3 treatment groups.

For the all Part 1 analyses, the analyses method and ITT/Efficacy population and their subsets were applied in the same manner as Part 2; 64 (100%), 60 (100%), 65 (100%) patients for ITT population and 58 (90.6%), 58 (96.7%), 59 (90.8%) patients for ITT for the 2nd treatment course in Main Study Period Subset, 61 (95.3%), 59 (98.3%), 61 (93.8%) patients for efficacy population and 57 (89.1%), 58 (96.7%), 57 (87.7%) patients for efficacy for the 2nd treatment course in Main Study Period Subset in the CT-P10, Mabthera and Rituxan, respectively.

In the efficacy population, for DAS28 (CRP), the 95% CIs of the differences between the CTP10 and Mabthera groups during the 1st treatment course were (-0.15, 0.46), (-0.18, 0.55), (- 0.06, 0.62), (-0.12, 0.57), (-0.46, 0.36) and (-0.56, 0.26) at Weeks 4, 8, 12, 16, 20 and 24, respectively. For the 2nd treatment course over the long-term period up to 48 weeks, the 95% CIs of the differences between the CT-P10 and Mabthera groups were (-0.43, 0.41), (-0.63, 0.29), (-0.51, 0.41) at Weeks 32, 40 and 48, respectively.

For DAS28 (ESR), the 95% CIs of the differences between the CT-P10 and Mabthera groups during the 1st treatment course were (-0.11, 0.53), (-0.18, 0.54), (-0.01, 0.70), (-0.17, 0.56), (- 0.31, 0.51) and (-0.44, 0.40) at Weeks 4, 8, 12, 16, 20 and 24, respectively. For the 2nd treatment course over the long-term period up

to 48 weeks, the 95% CIs of the differences between the CT-P10 and Mabthera groups were (-0.29, 0.55), (-0.47, 0.48), (-0.36, 0.61) at Weeks 32, 40 and 48, respectively.

The 95% CIs for the estimate of treatment differences of CT-P10 and MabThera were well within the range ± 0.60 for most of the time points, which is the pre-specified therapeutic margin applied to the primary endpoint of Study CT-P10 3.2 for Week 24 time-point, except points including Week 12 for DAS28 (CRP, ESR), Week 40 for DAS 28 (CRP) and Week 48 for DAS28 (ESR). However it should be noted that Part 1 was not powered or intended to demonstrate therapeutic equivalence given its smaller data set. The sample size of Part 1 was almost twice smaller than that of Part 2 and therefore no conclusions can be drawn in respect to some of the DAS28 response variability in this fragmented subset. Importantly, the DAS28 response variability did not follow any specific pattern and was not replicated in appropriately powered Part 2 demonstrating consistent and similar therapeutic responses through an entire 48 week treatment perio. Considering the above, it is concluded that there were no statistically significant differences at the 5% significance level since the 95% CIs included 0 in all cases.

Also, the same analysis has been carried out in the ITT population as a sensitivity analysis and the results were in line with that on the efficacy population

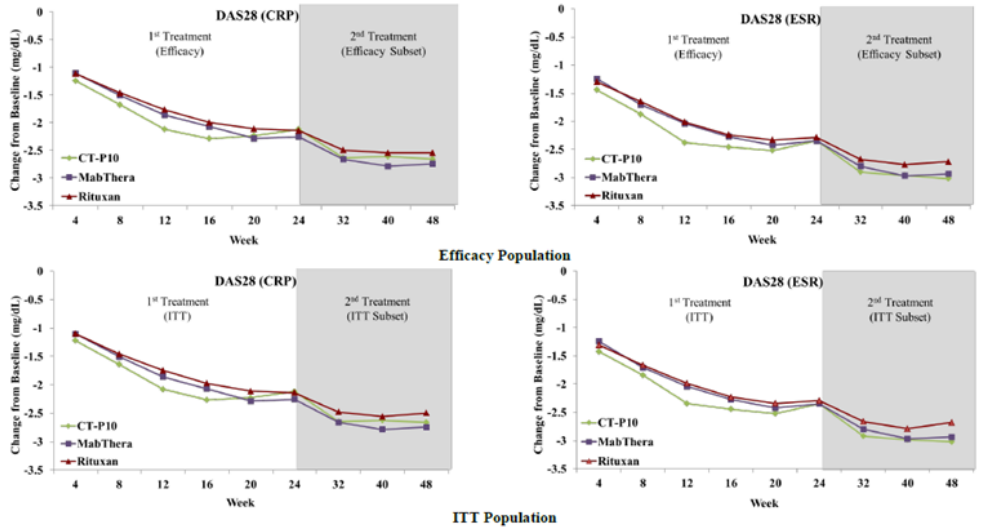
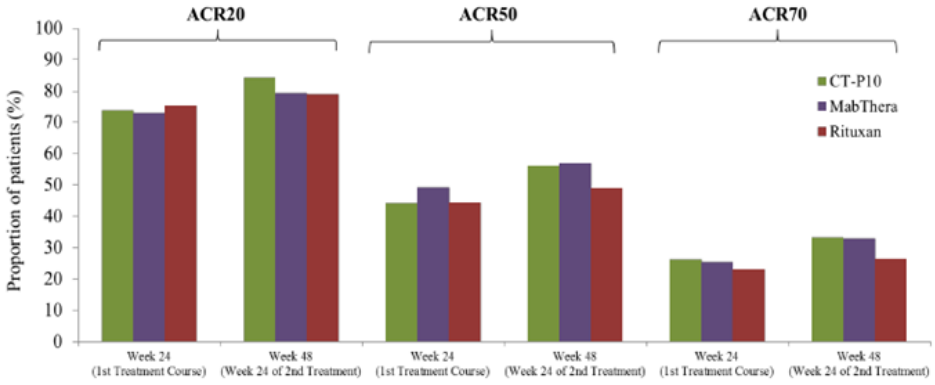


Figure 14: Mean Change from Baseline of DAS28 (CRP, ESR) up to Week 48 in Study CT-P10 3.2: Efficacy/ITT Population and Efficacy/ITT Population of 2nd Treatment Course in Main Study Period Subset – Part 1

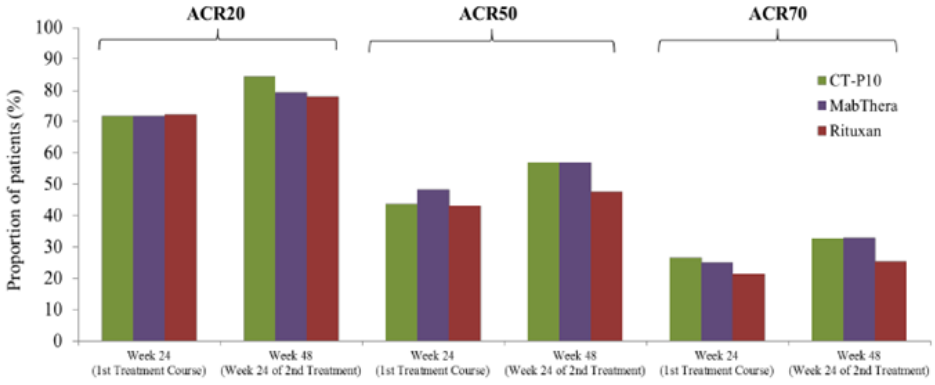
The long-term efficacy using ACR analyses were evaluated in Part 1 in the same manner as was performed for Part 2.

In the efficacy population, the proportions of patients achieving clinical responses according to the ACR20/50/70 criteria were similar between the CT-P10, Mabthera and Rituxan groups up to Week 48. The proportions increased until Week 20 and were maintained long-term up to Week 48 in the 3 treatment groups.

For ACR20, the 95% CIs of the differences between the CT-P10 and Mabthera groups during the 1st treatment course were (-0.25, 0.12) (-0.21, 0.15) (-0.28, 0.05) (-0.15, 0.16) (-0.20, 0.09) and (-0.17, 0.15) at Weeks 4, 8, 12, 16, 20 and 24, respectively. For the 2nd treatment course over the longer term period, up to 48 weeks, the 95% CIs of the differences were (-0.17, 0.10), (-0.10, 0.13) and (-0.19, 0.09) at Weeks 32, 40 and 48, respectively. The 95% CIs of these differences according to the ACR50 and ACR70 criteria were also similar between the CT-P10 and MabThera groups



Efficacy Population



ITT Population

Figure 15: 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 1

STUDY CT-P10 3.3

A Phase 1/3, Randomized, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison With Rituxan, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma (see section on Pharmacokinetics.)

- **Objectives**

The overall objective of this study was to demonstrate similar pharmacokinetics and non-inferior efficacy of CT-P10 compared to Rituxan. The study was divided into 2 parts, each of which assessed 1 of 2 primary endpoints, as follows:

Part 1: The primary objective of Part 1 of the study was to demonstrate that CT-P10 is similar to Rituxan in terms of pharmacokinetics as determined by area under the serum concentration-time curve at steady state (AUCtau) and maximum serum concentration at steady state (CmaxSS) at Core Cycle 4.

Part 2: The primary objective of Part 2 of the study will be to demonstrate that CT-P10 is noninferior to Rituxan in terms of efficacy as determined by overall response rate (ORR) (complete response [CR] + unconfirmed complete response [CRu] + partial response [PR]) over Cycle 8 (Core Study Period) according to the 1999

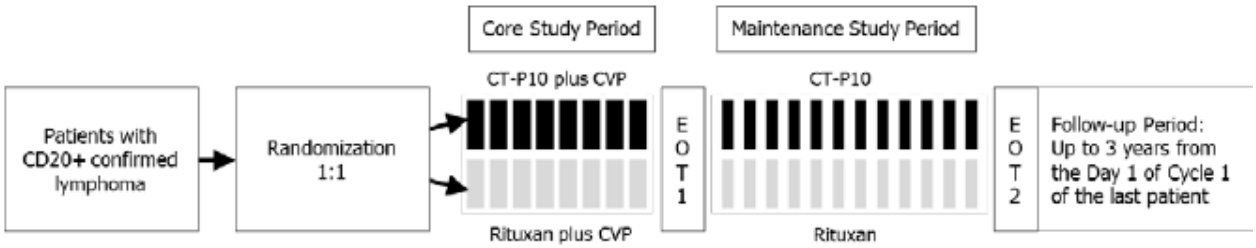
International Working Group (IWG) criteria in previously untreated patients with advanced (stage III-IV) CD20+ follicular lymphoma (FL).

The response evaluation listing includes information about date of evaluation, evaluation of target lesion, evaluation of nontarget lesion, evaluation of new lesion, bone marrow involvement, organ enlargement, LDH level, B-symptom, overall response evaluated, PD date, best overall response (BOR), and BOR date based on local review using 1999 IWG and 2007 IWG criteria by treatment group for the ITT population.

The primary efficacy endpoint for Part 2 will be the ORR (CR + CRu +PR) during the Core Study Period as per the 1999 IWG criteria. It should be noted that the non-inferiority margin was based on absolute point estimate difference and not using 95% CI approach.

- **Design**

Study Design Schematic



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

- **Patients**

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), at least 1 measurable tumor mass that had not previously been irradiated, confirmed CD20+ lymphoma, Ann Arbor stage III or IV disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate bone marrow, hepatic, and renal function reserve

- **Baseline characteristics**

Table 24: Ann Arbor Staging and FLIPI Score in Study CT-P10 3.3: ITT Population

	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)	Total (N=121)
Ann Arbor Staging at Screening, n (%)			
Principal stage			
Stage I	0	0	0
Stage II	0	0	0
Stage III	17 (28.8)	33 (53.2)	50 (41.3)
Stage IV	42 (71.2)	29 (46.8)	71 (58.7)
FLIPI Score at Screening, n (%)			
0	0	0	0
1	7 (11.9)	5 (8.1)	12 (9.9)
2	25 (42.4)	20 (32.3)	45 (37.2)
3	19 (32.2)	26 (41.9)	45 (37.2)
4	6 (10.2)	11 (17.7)	17 (14.0)
5	2 (3.4)	0	2 (1.7)
Follicular Lymphoma Grade At Screening, n (%)			
Grade 1[1]	18 (30.5)	18 (29.0)	36 (29.8)
Grade 2	31 (52.5)	29 (46.8)	60 (49.6)
Grade 3a	9 (15.3)	15 (24.2)	24 (19.8)
Grade 3b	0	0	0
Missing[2]	1 (1.7)	0	1 (0.8)

Sources: CSR CT-P10 3.3 Post-text Table 14.1.6 and Table 14.1.8

[1]For Patient 4201-3001, pathologic diagnosis was Grade 1 FL at Screening based on bone marrow, flow cytometry report and other available blood test. However, grade could not be assured as lymph node biopsy has not been performed. This patient was excluded from PP population due to this major protocol violation.

[2]The Patient 3204-3012 did not have source document to identify FL grade but FL were diagnosed with bone marrow specimen. This patient was excluded from PP population due to this major protocol violation

	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)	Total (N=121)
Ann Arbor Staging at Screening, n (%)			
Principal stage			
Stage I	0	0	0
Stage II	0	0	0
Stage III	17 (28.8)	33 (53.2)	50 (41.3)
Stage IV	42 (71.2)	29 (46.8)	71 (58.7)
FLIPI Score at Screening, n (%)			
0	0	0	0
1	7 (11.9)	5 (8.1)	12 (9.9)
2	25 (42.4)	20 (32.3)	45 (37.2)
3	19 (32.2)	26 (41.9)	45 (37.2)
4	6 (10.2)	11 (17.7)	17 (14.0)
5	2 (3.4)	0	2 (1.7)
Follicular Lymphoma Grade At Screening, n (%)			
Grade 1[1]	18 (30.5)	18 (29.0)	36 (29.8)
Grade 2	31 (52.5)	29 (46.8)	60 (49.6)
Grade 3a	9 (15.3)	15 (24.2)	24 (19.8)
Grade 3b	0	0	0
Missing[2]	1 (1.7)	0	1 (0.8)

[1]For Patient [redacted], pathologic diagnosis was Grade 1 FL at Screening based on bone marrow, flow cytometry report and other available blood test. However, grade could not be assured as lymph node biopsy has not been performed. This patient was excluded from PP population due to this major protocol violation.
[2]The Patient [redacted] did not have source document to identify FL grade but FL were diagnosed with bone marrow specimen. This patient was excluded from PP population due to this major protocol violation

- **Recruitment and populations**

	CT-P10 (N=59)	Rituxan (N=62)	Total (N=121)
	Number (%) of Patients		
Initiated core study treatment[3]	59 (100.0)	62 (100.0)	121 (100.0)
Completed up to and including Core Cycle 4	55 (93.2)	58 (93.5)	113 (93.4)
Discontinued before Core Cycle 5	4 (6.8)	4 (6.5)	8 (6.6)
Primary reason for discontinuation			
Progressive disease[4]	2 (3.4)	1 (1.6)	3 (2.5)
Adverse event (angina pectoris)[5]	1 (1.7)	0	1 (0.8)
Patient died (tumor lysis syndrome)[6]	1 (1.7)	0	1 (0.8)
Withdrew consent	0	2 (3.2)	2 (1.7)
Investigator decision[7]	0	1 (1.6)	1 (0.8)
Number of deaths	2 (3.4)	0	2 (1.7)
Reason for death			
Progressive Disease[8]	1 (1.7)	0	1 (0.8)
Adverse event (tumor lysis syndrome)[6]	1 (1.7)	0	1 (0.8)

Abbreviation: ITT, intent-to-treat.

	CT-P10 (N=59)	Rituxan (N=62)	Total (N=121)
	Number (%) of Patients		
Total number of patients in Part 1			
Screened			159
Primary reason for screening failure			
Inclusion/exclusion criteria not met			30
Patient withdrew consent			3
Other			5
Randomized	59 (100.0)	62 (100.0)	121 (100.0)

Initiated core study treatment	59 (100.0)	62 (100.0)	121 (100.0)
Completed up to and including Core Cycle 4	55 (93.2)	58 (93.5)	113 (93.4)
Discontinued before Core Cycle 5	4 (6.8)	4 (6.5)	8 (6.6)
Primary reason for discontinuation			
Progressive disease	2 (3.4)	1 (1.6)	3 (2.5)
Adverse event (angina pectoris)	1 (1.7)	0	1 (0.8)
Patient died (tumor lysis syndrome)	1 (1.7)	0	1 (0.8)
Withdrew consent	0	2 (3.2)	2 (1.7)
Investigator decision	0	1 (1.6)	1 (0.8)
Number of deaths	2 (3.4)	0	2 (1.7)
Reason for death			
Progressive Disease	1 (1.7)	0	1 (0.8)
Adverse event (tumor lysis syndrome)	1 (1.7)	0	1 (0.8)

Abbreviation: ITT, intent-to-treat.

Table 10-2 Major Protocol Deviations and Other Categories Used for Exclusion: ITT Population

	CT-P10 (N=59)	Rituxan (N=62)	Total (N=121)	Excluded Populations[1]
	Number (%) of Patients			
Major protocol deviations				
Noncompliance with I/E criteria	2 (3.4)	0	2 (1.7)	PP
Other reasons for exclusion				
No posttreatment PD results	1 (1.7)	1 (1.6)	2 (1.7)	PD

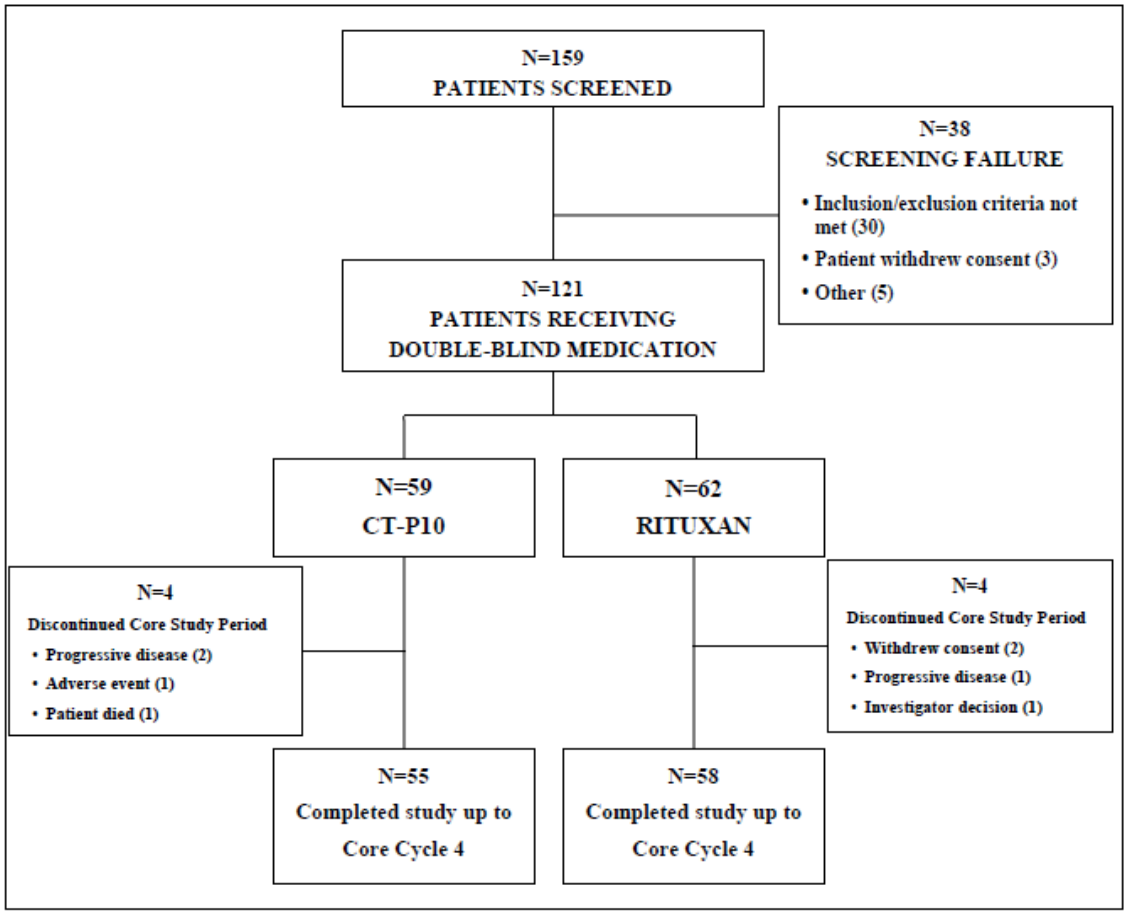
Abbreviations: I/E, inclusion/exclusion; ITT, intent-to-treat; PD, pharmacodynamic; PP, per protocol.

All patients in the CT-P10 and Rituxan treatment groups were included in the ITT population. The proportion of patients in each of the other analysis populations was similar between the 2 treatment groups.

Table 21: Analysis Populations of Study CT-P10 3.3

Population	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of patients		
Intent-To-Treat	70 (100.0)	70 (100.0)	140 (100.0)
PP	66 (94.3)	68 (97.1)	134 (95.7)
Safety	70 (100.0)	70 (100.0)	140 (100.0)

Figure 10-1 Patient Disposition



- **Outcomes**

Primary Efficacy Endpoint

In the PP population, based on central review, the proportions of patients achieving overall response (CR+CRu+PR) according to 1999 IWG criteria were 97.0% (64/66 patients) and 92.6% (63/68 patients) in the CT-P10 and Rituxan groups, respectively (Table 22). The difference between the groups of the ORR according to the 1999 IWG criteria was 4.3% and lies on the positive side of the pre-defined non-inferiority margin using a point estimate difference of -7% based on reference product variability which was defined in the protocol.

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)	-

[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

Table 23: Proportion of Patients Achieving ORR (CR + CRu + PR) over Cycle 8 (Core Week 24) According to the 1999 IWG Criteria in Study CT-P10 3.3: ITT population - Central Review

Number of patients (%)	CT-P10 (N=70)	Rituxan® (N=70)	Difference[1]
ORR (CR + CRu + PR)	67 (95.7)	63 (90.0)	(5.7)
CR	21 (30.0)	15 (21.4)	-
CRu	6 (8.6)	8 (11.4)	-
PR	40 (57.1)	40 (57.1)	-

[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

Additional Efficacy Parameters

Bone marrow assessments and B-symptoms assessments were performed and the results were similar between the 2 treatment groups. In the bone marrow assessments, bone marrow involvement at screening was reported for 78 (55.7%) patients (45 [64.3%] patients and 33 [47.1%] patients in the CT-P10 and Rituxan groups, respectively). Slight chance driven baseline difference in bone marrow difference, nevertheless, had not influenced similarity in overall response. Among these 78 patients who reported positive at screening, 39 patients returned to negative at post-treatment visits (22 patients in the CT-P10 group and 17 patients in the Rituxan group, respectively). There were no differences found between the 2 treatment groups and there were no patients who newly reported positive for bone marrow test at post-treatment visits. In the B-symptoms results, the number of patients with at least 1 B-symptom at screening was 37 (26.4%) patients (17 [24.3%] patients and 20 [28.6%] patients in the CT-P10 and Rituxan groups, respectively). At EOT1, B-symptoms were present in only 1 (1.4%) patient in the CTP10 group, and the patient was evaluated as partial response (PR) at EOT1. There were no notable differences between the 2 treatment groups.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development encompasses a Phase 1 PK equivalence study between CT-P10 and the EU reference product (MabThera) in patients with RA (Study CT-P10 1.1), followed by a therapeutic equivalence Phase 3

study in RA patients (Study CT-P10 3.2). The Phase 3 study consists of 2 parts, i.e., part 1 is designed to evaluate 3-way PK equivalence of CT-P10 against reference products, Mabthera and Rituxan, whereas part 2 is aimed at establishing therapeutic equivalence between CT-P10 and reference rituximab (MabThera/Rituxan) (Study CT-P10 3.2). The Phase 1 PK equivalence Study CT-P10 1.1 in RA patients has an extension to assess long-term safety and efficacy up to Week 104 (Study CT-P10 1.3). This clinical data package is further supported by preliminary data from 1 study in an oncology indication, i.e., a Phase 1/3 PK equivalence study between CT-P10 and Rituxan in patients with AFL (Study CT-P10 3.3).

Study CT-P10 1.1 is a phase 1, randomised, controlled, multicentre, 2-Arm, parallel-group, double-blind study to demonstrate the equivalence of CT-P10 to Mabthera with respect to the PK profile in patients with RA. This setting is considered a sensitive clinical model to detect potential efficacy differences between CT-P10 and MabThera. The study population consisted of male and female patients with active RA who experienced an inadequate response to previous or current treatment with the TNF inhibitors infliximab, golimumab, adalimumab or etanercept, or was intolerant to at least 1 administration of these agents. However, MabThera is authorised in patients with severe, active RA who have had an inadequate response or intolerance to other DMARD including 1 or more TNF inhibitor therapies, whereas the inclusion criteria for the CT-P10 1.1 study allow the recruitment of patients with moderate to severe RA. In this perspective, the efficacy data from the subset of patients with ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed) matching the inclusion criterion of the REFLEX and DANCER studies, have been evaluated in the post-hoc analysis.

Efficacy was assessed by the evaluation of the ACR criteria (individual components, ACR20, ACR50, and ACR70, time to onset of ACR20, and hybrid ACR response), mean decrease in DAS28, EULAR response criteria, CDAI, SDAI, joint damage progression (radiographic evaluations, Sharp/van der Heijde modified score), general health status (Medical Outcome Study Short-Form Health Survey [SF-36]), and functional disability (HAQ). From a clinical view these are standard endpoints, mainly based on ACR criteria and DAS28, which is agreed. The joint damage and EULAR response status are of value. The ACR20, 50, 70 and DAS28 parameters are assessed at 8-week intervals up to Week 24. This was agreed with the SAWP so as to be able to detect differences between the treatments. Nevertheless, all the efficacy endpoints are secondary variables in this study.

The study CT-P10 1.1 was powered to demonstrate PK equivalence of CT-P10 and MabThera in AUC0-last and Cmax. No sample size calculations based on efficacy were carried out. However, the statistical comparison of both products has been carried out in a post-hoc way. The primary objective of the post-hoc-analyses was to investigate the therapeutic equivalence for DAS28 between CT-P10 and Mabthera at Week 24 in the study CT-P10 1.1. According to the company, in order to determine an appropriate equivalence margin for DAS28, a literature search of DAS28 responses with rituximab in RA patients who had inadequate response to one or more TNF antagonist therapies was carried out. In the DANCER study (Emery et al., 2006), analysis of variance showed the adjusted mean change in DAS28 from baseline to be significantly greater in patients treated with rituximab (2 x 500 mg, 2 x 1000 mg) than in patients treated with placebo (- 1.79 and -2.05 vs. -0.67). In the pivotal REFLEX study (Cohen et al., 2006) the mean change from baseline in the DAS28 score was -1.9 in the rituximab arm vs. -0.4 in the placebo arm, corresponding to a treatment difference of 1.5. As advised by the CHMP (EMA/CHMP/SAWP/78796/2014), a properly chosen equivalence margin should exclude clinically relevant effects. The EULAR response criteria define a change in DAS28 of up to 0.6 points within an individual as 'no improvement' (Fransen et al., 2005). In line with SAWP/CHMP recommendations, margin of ± 0.6 for the post-hoc analysis of therapeutic equivalence in CT-P10 1.1 study and pre-defined equivalence in CT-P10 3.2 study has been employed. From a clinical perspective the use of DAS28 as main variable when it comes to assessing the similarity is endorsed and moreover if in addition to the analysis based on DAS28, the individual components of ACR criteria are also compared between treatments.

Study 3.2 is a randomised, controlled, double-blind, parallel-group, Phase 3 study to compare the PK, efficacy and safety between CT-P10, Rituxan and Mabthera in Patients with rheumatoid arthritis (RA). Part 1 was designed for demonstration of 3-way PK equivalence between CT-P10 and Mabthera, CT-P10 and Rituxan, Mabthera and Rituxan. Part 2 was intended to demonstrate therapeutic equivalence between CT-P10 and the combined reference products, Mabthera and Rituxan in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by DAS28 (CRP) at Week 24. The Extension Study Period, which was designed to evaluate additional safety and immunogenicity, was initiated between Week 48 and Week 52 of the entire study period and was up to 76 weeks after the Week 0 infusion.

Study 3.3 is a Phase 1/3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with cyclophosphamide, vincristine and prednisone (CVP) in patients with Advanced Follicular Lymphoma (AFL). The primary efficacy endpoint for Study CT-P10 3.3 assessed in Part 2 of the study is the ORR (CR + CRu + PR) according to 1999 IWG criteria over Cycle 8 in Part 2 which is an accepted endpoint in this setting.

Efficacy data and additional analyses

Overall, demographic characteristics in the study CT-P10 1.1 were well balanced between the 2 treatment groups. The mean ± SD age of patients was 49.8 ± 12.54 years in the CT-P10 group and 51.3 ± 10.86 years in the Mabthera group. In total, there were fewer male patients than female patients (19 [12.3 %] male patients compared with 135 [87.7 %] female patients). The majority of patients were white (105 [68.2 %] patients). The mean ± SD body mass index of patients was 27.11 ± 6.04 kg/m2 in the CT-P10 group and 27.53 ± 5.46 kg/m2 in the Mabthera group. Generally speaking, both groups are evenly balanced and the slight differences should not be critical in terms of efficacy.

Regarding efficacy results, overall, both treatments are similar in terms of ACR. The proportion of subject who achieved ACR 20 in CT-P 10 and MabThera respectively was 57.0% and 54.2 %, at Week 8; 70.0% and 68.8% patients at Week 16 and 63.0% and 66.7 % at Week 24. Results are pretty similar if ACR 50 and 70 are looked. Regarding the individual components of the ACR criteria, all the items analysed show a comparable result (mean number of tender joints, mean number of swollen joints, mean VAS scores for the patient assessment of pain, mean VAS scores for the patient and physician global assessment of disease activity, mean score for the HAQ estimate of physical ability, CRP and ESR).

The time of onset of ACR20 response is also similar between CT-P10 and MabThera with medians of 58.0 and 60.0 days, respectively. Regarding the change from baseline in the disease activity measured by DAS28 in Study CT-P10 1.1, the post-hoc analysis carried out by the applicant meets the equivalence therapeutic according to the equivalence margin of 0.60.

More patients were re-treated after Week 24 and before Week 48 of the Main Study in the CT-P10 arm (58%) than in the MabThera arm (45%). It is agreed that the decision for re-treatment is multifactorial but, as the study was blinded, there should not be any significant bias to explain this observation; moreover eligibility criteria for re-treatment were met in the same proportion of patients and furthermore, the proportion of patients that were re-treated despite being ineligible was also higher in the CT-P10 arm than in the MabThera arm. Finally, the time to re-treatment estimated throughout the whole trial was shorter in the CT-P10 arm than in the MabThera arm; this difference is not statistically significant.

The Applicant conducted ANCOVA analyses of DAS28 in the all-randomised/treated population (ITT analysis) and efficacy population (PP analysis) of Study CT-P10 1.1 using baseline value as a covariate. Missing data and

data for visits after retreatments were imputed using baseline observation carried forward (BOCF) for all-randomised/treated population. These analyses showed, in both ITT and PP populations, equivalent efficacy up to week 32 but indicated slightly lower efficacy at the last time points. However, it is accepted that there is no statistically significant difference between the two products.

In order to support the equivalence of the two products, comparative ITT and PP (efficacy population) analyses were performed with estimates calculated for the differences in ACR rates between treatments and their 95% confidence intervals at Core Weeks 8, 16, 24, 32, 40 and 48. For the ITT analysis weeks with missing data or after re-treatment were treated as non-response. Results from these analyses show that the ACR20 rates were broadly comparable between the two treatment arms except at week 48 (lower for CT-P10, with 95%CI of the difference being [-23%; +5%]). The study was not powered to show equivalence and no equivalence margins were predefined. Even at week 24, the 95%CI of the difference would seem rather wider [-17%; +16%] than clinically acceptable. Nevertheless, all 95%CI included 100%. In the PP analysis, the ACR20 rates were broadly comparable between the two treatment arms except at weeks 24 and 48 (lower for CT-P10, with 95%CI of the difference being [-22%; +11%] and [-33%; +23%]). The ACR50 rates were broadly comparable between the two treatment arms.

In addition, efficacy data from Study CT-P10 1.1 were compared to historical data from the pivotal Phase 3 registration study REFLEX for MabThera and the supportive Phase 2b registration study DANCER. Overall, the comparison among the different studies and subgroups showed an apparent similarity between CT-P 10 and MabThera.

In the study CT-P10 1.3, similar conclusions could be achieved regarding the equivalence of CT-P10 and MabThera. The clinical response in terms of ACR and DAS28 seems similar between groups. However this is a descriptive analysis and due to the sample size no firm conclusions can be drawn.

Regarding the study 3.2, in the efficacy population, the 95% CIs for the estimate of treatment difference was within the equivalence margin of 0.6 (in terms of change from baseline in DAS28 (CRP) at Week 24). A similar result was found in change from baseline of DAS28 (ESR), showing no significant difference between CT-P10 and reference products groups. Also, the same analysis has been carried out in the all-randomised population as a sensitivity analysis and the results were in line with that of efficacy population. In contrast to study CT-P10 1.1, study CT-P10 3.2 involved systematic retreatment at week 24, except for safety reasons (which occurred in 4 patients; 1%). The proportion of patients that completed two treatment courses was roughly comparable across treatment arms: 87% (CT-P10), 89% (Rituxan); 93% (MabThera). The main reason for discontinuation, especially for CT-P10, was withdrawal of consent.

Focusing on the results from the study 3.2, as the number of excluded patients was small, analyses in the efficacy and ITT populations provide very similar results. In Part 1 and 2 combined, DAS28 differences (without imputation) appeared marginally in favour of CT-P10 during the 24 weeks following the second treatment course and in line with the results after the first treatment course. Their 95% confidence intervals lied within the pre-defined limits of ± 0.6.

Likewise, the ACR responses (missing data imputed as failures) were very similar for CT-P10 and the reference products during the 24 weeks following the second treatment course with all 95% confidence intervals within ± 0.15.

The results of the patients randomised to the three treatment arms in Part 1 showed a favourable trend for CT-P10 compared to both reference products during the first weeks after the first treatment course, which tapered by weeks 20-24; after the second treatment course, the results of CT-P10 and MabThera were

comparable, and slightly better than those of Rituxan. The ACR responses were very similar between the three treatment arms with no consistent trend.

Study CT-P10 3.3 is a supportive study to confirm biosimilarity in oncology and subsequently the extrapolation of the indications of rituximab in oncology. Baseline characteristics do not reveal important differences between groups. The population analysed in part 2 (efficacy) is evenly balanced between groups. A total of 184 patients were screened for enrollment in Part 2. One hundred forty patients were randomly assigned to study drug and initiated the Core study treatment (70 patients in each treatment group). 62 subjects completed the core study (part 2). The reasons for discontinuation from the core period are overall balanced between CT-P10 and Rituxan arms, with 8 patients in each group. Major protocol deviations and other categories used for exclusion from ITT population do not seem to have an impact on the results (in total, 6 patients (4 [5.7%] patients in the CT-P10 treatment group and 2 [2.9%] patients in the Rituxan treatment group) were excluded from the PP population for the primary efficacy endpoint).

Demographic characteristics seem to be evenly balanced (age: 57 vs 58.5; ECOG 0-1: 98.6% vs 98.5). The mean (SD) disease duration of lymphoma was 3.43 (7.283) months in the CT-P10 treatment group and 2.35 (2.907) months in the Rituxan treatment group. Follicular lymphoma CD20+ was confirmed in all patients in both groups. The most commonly reported FL grade at the time of screening was FL grade 2 (36 [51.4%] patients in the CT-P10 treatment group and 34 [48.6%] patients in the Rituxan treatment group). Nevertheless, there are some imbalances in Ann Arbor Stage. At the time of screening, patients in Ann Arbor Stage III were 30% vs 51.4% and Ann Arbor Stage III 70% vs 48.6% CT-P10 vs Rituxan respectively. Regarding FLIPI score, there are slight differences between groups, overall with a greater percentage of patients in FLIPI scores 3-4 in Rituxan than in CT-P10 (60% vs 47.2% respectively). This difference seem to be driven by the nodal involvement, with 65.7% and 84.3% of patients with a number of nodal sites >4 (CT-P10 vs Rituxan respectively) and not seem to play a critical role in the conclusion.

Focusing on the efficacy results of the part 2, only ORR according to 1999 IWG criteria has been submitted. ORR as per the 2007 IWG criteria, time-to-event parameters including PFS, TTP, TTF, response duration, DFS and OS, and follow-up duration will be included in the final report of the study.

ORR is an acceptable endpoint for this application of biosimilarity in follicular lymphoma indication. The company has established an equivalence margin of 7%, even though and according to the company the non-inferiority margin was based on absolute point estimate difference and not using 95% CI approach. The 7% is apparently based on an expected ORR of 81% (Marcus et al. 2005). In this study MabThera showed 81% CR + CRu + PR (n=162) compared with CVP alone, which showed a 57% response rate (n=159). In another study an ORR of 88% was reported in patients in the R-CVP treatment arm (Federico et al 2013). Considering this 7% difference in the ORR compared to the previous historical data used (Marcus et al 2005), a 7% non-inferiority margin has been selected to assess efficacy (in the CT-P10 3.3 study, an ORR of 81% has been selected as the point estimate for the sample size calculation). These calculations are in accordance the EMA Guidance Choice of Non-inferiority Margin and acceptable from a clinical perspective. On analysing the ORR (central review) both in PP and ITT population, the difference lies within 7% (4.3% and 5.7% PP and ITT respectively). ORR appears slightly superior to CT-P10 (97% vs 92.6% and 95.7% vs 90.0% CT-P10 vs Rituxan PP and ITT respectively). The pattern of the responses points out towards more CR and similar PR, but the number of unconfirmed CR could change these values. The lower bound for 95%CI both in PP and ITT would lie within 7% (ORR difference: PP population 4.3% [95%CI -4.14; 13.33] ITT population 5.7% [95%CI -3.4; 15.4]). However as 7% is considered a very conservative margin, seeing as outlined above the half of the differences between the R-CVP and CVP in ORR (Marcus et al 2005) would be 12%; and considering the sample size of study CT-P10 3.3, it is plausible that with a bigger sample size, the CI had been narrower.

Analyses carried out according to ADA status reveal similar outcomes to the main ones. No data on ORR as per the 2007 IWG criteria, time-to-event parameters including PFS, TTP, TTF, response duration, DFS and OS have been submitted. PFS and OS analyses will be submitted in the final CSR (see RMP) and as yearly updates as patients who experienced CR, CRu, or PR after Cycle 8 of the Core Study Period will enter in the Maintenance Study Period with rituximab only.

2.4.4. Conclusions on the clinical efficacy

Biosimilarity of CT-P10 and MabThera is considered demonstrated based on the efficacy data. In the pivotal RA trial, efficacy results in terms of DAS28 and ACR were shown to be comparable between CT-P10 and MabThera. In addition, PK data discussed support the extrapolation to the autoimmune indications MPA/GPA.

The objectives of study CT-P10 3.3 were to demonstrate similarity in pharmacokinetics and non-inferiority in efficacy of CT-P10 to Rituxan as primary endpoints when coadministered with CVP in patients with advanced FL; these objectives have been met and furthermore, extrapolation in the context of NHL and CLL indications is acceptable.

2.5. Clinical safety

The clinical development programme comprises for CT-P10 six studies, including maintenance studies. As of this date, two clinical studies have been completed, one has been terminated, two are ongoing, and one is planned. The completed studies comprise a randomised, controlled comparison of the pharmacokinetics, efficacy and safety of patients with rheumatoid arthritis treated with up to two courses of CT-P10 or MabThera (Study CT-P10 1.1), and an open-label maintenance study in which eligible subjects from Study CT-P10 1.1 were treated with CT-P10 for a total cumulative observation interval in both studies for each subject of up to 104 weeks (Study CT-P10 1.3).

A pilot Phase 1, open-label and single-arm study, CT-P10 1.2, in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) was initiated but prematurely terminated due to recruitment issues after 1 patient had been enrolled. In addition, 3 Phase 3 studies are currently ongoing, which are Study CT-P10 3.2 in RA patients, Study CT-P10 3.3 in advanced follicular lymphoma (AFL) patients and Study CT-P10 3.4 in low tumour burden follicular lymphoma (LTBFL) patients. Among the ongoing Phase 3 studies, the data from Studies CT-P10 3.2 (up to Week 24 in Part 1 and Part 2 patients) and CT-P10 3.3 (up to Core Cycle 8 [24 weeks] in Part 2 patient) is now available. The result of Study CT-P10 3.4, which has been designed to assess therapeutic similarity in patients with LTBFL, will be available by 2021.

The completed studies comprise a randomised, controlled comparison of the pharmacokinetics, efficacy and safety of patients with rheumatoid arthritis treated with up to two courses of CT-P10 or MabThera (Study CT-P10 1.1), and an open-label maintenance study in which eligible subjects from Study CT-P10 1.1 were treated with CT-P10 for a total cumulative observation interval in both studies for each subject of up to 104 weeks (Study CT-P10 1.3).

In the clinical studies with CT-P10, the current safety population consists of 666 patients who were treated with at least 1 dose (full or partial) of CT-P10, Mabthera or Rituxan during any dosing period. For RA indication, safety data in a total of 525 patients are available; up to 104 weeks throughout Studies CT-P10 1.1 and CT-P10 1.3 and up to 24 weeks in Study CT-P10 3.2 (Part 2). This includes the limited safety data from 20 patients in Study CT-P10 1.3 who switched from Mabthera to CT-P10. Study CT-P10 3.3 provides additional safety data in an oncology indication (140 patients with AFL).

Patient exposure

Exposure data are presented for completed studies only. The safety population consisted of all patients who received at least 1 (full or partial) dose of study drug (CT-P10 or Mabthera) during any study period (Core or Extension). A total of 122 subjects with rheumatoid arthritis were exposed to CT-P10 and 51 to MabThera. The safety population of Study CT-P10 1.1 included 153 patients (102 patients and 51 patients in the CTP10 and Mabthera groups, respectively). A total of 87 patients who had completed the main Study CT-P10 1.1 were enrolled into maintenance study, CT-P10 1.3. Of those patients, 38 (65.5%) patients and 20 (69.0%) patients were treated with CT-P10 in the maintenance and switch groups, respectively. A total of 102 subjects received at least one dose of CT-P10 in Study CT-P10 1.1 and a total of 58 patients received at least one dose of CT-P10 in maintenance study, Study CT-P10 1.3.

The mean (SD) total number of doses received in Study CT-P10 1.1 was 3.2 (1.00) doses and 2.8 (1.01) doses in the CT-P10 and Mabthera groups, respectively. The mean (SD) total number of does received was similar between the 2 treatment groups in the Core Study Period (2.0 [0.10] doses and 2.0 [0.14] doses in the CT-P10 and Mabthera groups, respectively) and in the Extension study Period (2.0 [0.13] doses and 1.9 [0.29] doses for the CT-P10 and Mabthera groups, respectively). The mean (SD) total dose administered was similar between the 2 treatment groups (3142.56 [1004.55] mg and 2843.14 [1007.42] mg in the CT-P10 and Mabthera groups, respectively).

In Study CT-P10 1.3, the mean (SD) total number of doses of CT-P10 was 2.0 (0.30) doses overall and was similar in the CT-P10 maintenance and the CT-P10 switch groups (2.0 [0.37] doses and 2.0 [0.00] doses, respectively).

The patient exposure and follow-up duration are presented below.

Overall exposure – Safety population

Study CT-P10 1.1

	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
	Overall Exposure – Number of Patients		
Core Week 0	102	51	153
Core Week 2	101	50	151
Extension Week 0	60	23	83
Extension Week 2	59	21	80

Study CT-P10 1.3

	CT-P10 Maintenance 1000 mg (N=58)	CT-P10 Switch 1000 mg (N=29)	Total (N=87)
	Overall Exposure - Number of Patients		
Treatment Period 1 Week 0	38	20	58
Treatment Period 1 Week 2	37	20	57
Treatment Period 2 Week 0	1	0	1
Treatment Period 2 Week 2	1	0	1

Follow-up duration in Studies CT-P10 1.1 and CT-P10 1.3 – Safety population

Duration of Exposure	CT-P10 1000mg						MabThera® 1000mg	
	Total		CT-P10 Only		Switched from MabThera®[1]			
	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)	Subjects (n)	Subject-time (days)
Total	122	51472	102	47167	20	4305	51	18500
≤ 6 months	16	2217	7	779	9	1438	4	346
> 6 months - ≤ 12 months	36	11045	25	8178	11	2867	24	7835
> 12 months - ≤ 18 months	42	20163	42	20163	0	0	23	10319
> 18 months - ≤ 24 months	28	18047	28	18047	0	0	0	0

Note: Month = 30.4375 days

[1] Subjects switched to CT-P10 between 24 and 80 weeks after MabThera® treatment.

Table 25: Overall Exposure to CT-P10, Mabthera or Rituxan Up to Week 24 in Study CT-P10 3.2 (Part 2): Safety Population

	CT-P10 1000 mg (N=161)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=151)	MabThera® + Rituxan® 1000 mg (N=211)	Total (N=372)
	Overall Exposure – Number of Patients				
Main Week 0	161	60	151	211	372
Main Week 2	154	59	147	206	360

Note: Twelve patients did not receive full dose of 2,000 mg; 4 (1.1%) patients withdrew consent (3 [1.9%] patients in the CT-P10 group and 1 [0.5%] patient in reference products group), 2 (1.2%) patients in CT-P10 group had significant or major protocol violation. Six (1.6%) patients received less than 1,000 mg and were discontinued due to an event of IRR; 2 [1.2%] patients in CT-P10 group and 4 [1.9%] patients in reference products group.

In the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), overall exposure estimated with the completed treatment courses of each patient is presented in Table 26.

Table 26: Overall Exposure (Number of Patients Receiving Dose) in CT-P10 RA Studies (CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2): Safety Population

	CT-P10 1000 mg			MabThera® + Rituxan® 1000 mg
	Total	CT-P10 Only	Switched to CT-P10[1]	
	Number (%) of Patients			
1st Course, infusion 1	283 (100.0)	263 (100.0)	20 (100.0)	262 (100.0)
1st Course, infusion 2	275 (97.2)	255 (97.0)	20 (100.0)	256 (97.7)
2nd Course, infusion 1	73 (25.8)	73 (27.8)	0	23 (8.8)
2nd Course, infusion 2	71 (25.1)	71 (27.0)	0	21 (8.0)
3rd Course, infusion 1	25 (8.8)	25 (9.5)	0	0
3rd Course, infusion 2	25 (8.8)	25 (9.5)	0	0
4th Course, infusion 1	1 (0.4)	1 (0.4)	0	0
4th Course, infusion 2	1 (0.4)	1 (0.4)	0	0

[1] Subjects switched to CT-P10 between 48 and 80 weeks after MabThera® treatment.

Study CT-P10 3.3 in the AFL population consists of the following periods: Screening Period (up to 4 weeks), Core Study Period (up to 8 cycles), Maintenance Study Period (up to 2 years) and Follow-up Period (until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient). Drug exposure to CT-P10 are summarized for the safety population. Safety data over 8 cycles of the Core Study Period were presented. For patients who were early discontinued before the completion of the Core Study Period, all collected data regardless of study period are included in the listings for this CSR. The majority of patients in each treatment group had study drug (CT-P10 or Rituxan) administered for all 8 cycles during the Core Study Period (62 [88.6%] patients in each treatment group). During the Core Study Period, the mean (SD) relative dose intensity (%) was similar between the 2 treatment groups (97.7 [4.40] and 98.3 [2.71] in the CT-P10 and Rituxan treatment groups, respectively).

Table 27: Overall Exposure to CT-P10 or Rituxan up to Core Cycle 4 in the Part 1 of Study CT-P10 3.3: Safety Population

	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)	Total (N=121)
	Overall Exposure - Number of Patients		
Core Cycle 1 at Week 0	59	62	121
Core Cycle 2 at Week 3	58	60	118
Core Cycle 3 at Week 6	57	58	115
Core Cycle 4 at Week 9	56	58	114

Table 28: Summary of Study Drug Exposure: Safety Population Study CT P10 3.3.

	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Number of patients who administered dose at each cycle			
Reason for not receiving CT-P10/Rituxan			
Core Cycle 1	70 (100.0)	70 (100.0)	140 (100.0)
Core Cycle 2	69 (98.6)	68 (97.1)	137 (97.9)
Death (Tumour lysis syndrome)	1 (1.4)	0	1 (0.7)
Patient withdrew consent	0	2 (2.9)	2 (1.4)
Core Cycle 3	68 (97.1)	66 (94.3)	134 (95.7)
Patient developed progressive disease	1 (1.4)	1 (1.4)	2 (1.4)
Investigator decision (No response)[1]	0	1 (1.4)	1 (0.7)
Core Cycle 4	66 (94.3)	66 (94.3)	132 (94.3)
Adverse event (Angina pectoris, Post procedural fistula)	2 (2.9)	0	2 (1.4)
Core Cycle 5	64 (91.4)	65 (92.9)	129 (92.1)
Patient developed progressive disease	1 (1.4)	1 (1.4)	2 (1.4)
Adverse event (Infusion-related reaction)	1 (1.4)	0	1 (0.7)
Core Cycle 6	63 (90.0)	64 (91.4)	127 (90.7)
Adverse event (Tuberculosis)	0	1 (1.4)	1 (0.7)
Patient withdrew consent	1 (1.4)	0	1 (0.7)
Core Cycle 7	62 (88.6)	63 (90)	125 (89.3)
Adverse event (Liver function test abnormal)	1 (1.4)	0	1 (0.7)
Investigator decision (as per site practice)[2]	0	1 (1.4)	1 (0.7)
Core Cycle 8	62 (88.6)	62 (88.6)	124 (88.6)
Patient developed progressive disease	0	1 (1.4)	1 (0.7)
Actual dose intensity (mg/m^2/week) during 8 cycles			
n	70	70	140
Mean (SD)	122.1 (5.54)	122.9 (3.37)	122.5 (4.59)
Median (minimum, maximum)	124.3 (94, 127)	123.9 (114, 130)	124.0 (94, 130)
Relative dose intensity (%) during 8 cycles			
n	70	70	140
Mean (SD)	97.7 (4.40)	98.3 (2.71)	98.0 (3.66)
Median (minimum, maximum)	99.3 (76, 102)	99.0 (91, 104)	99.2 (76, 104)
Number of patients with cycle delayed			
Core Cycle 2	3 (4.3)	3 (4.3)	6 (4.3)
Core Cycle 3	4 (5.7)	0	4 (2.9)
Core Cycle 4	2 (2.9)	2 (2.9)	4 (2.9)
Core Cycle 5	3 (4.3)	9 (12.9)	12 (8.6)
Core Cycle 6	5 (7.1)	5 (7.1)	10 (7.1)
Core Cycle 7	5 (7.1)	3 (4.3)	8 (5.7)
Core Cycle 8	5 (7.1)	4 (5.7)	9 (6.4)
Number of patients with dose interruption (or prolonged)			
Core Cycle 1	12 (17.1)	12 (17.1)	24 (17.1)
Core Cycle 2	1 (1.4)	2 (2.9)	3 (2.1)
Core Cycle 3	2 (2.9)[3]	0	2 (1.4)
Core Cycle 4	1 (1.4)	1 (1.4)	2 (1.4)
Core Cycle 5	1 (1.4)	0	1 (0.7)
Core Cycle 6	0	0	0
Core Cycle 7	1 (1.4)	0	1 (0.7)
Core Cycle 8	1 (1.4)	0	1 (0.7)

Note: Included patients who received at least 1 dose (full/partial) of study drug over 8 cycles of the Core Study Period.

1. Patient [redacted] discontinued from the Core Study Period since the investigator considered this patient showed insufficient response to the study treatment.
2. Patient [redacted] discontinued from the Core Study Period by the investigator's decision. The investigator decided to stop the treatment after Core Cycle 6 according to their routine practice since the overall response was stable disease.
3. All patients with dose interruption or prolonged of study drug infusion received full dose of prescribed dose but only 1 patient ([redacted]) in the CT-P10 treatment group received partial dose at Core Cycle 3 due to IRR (anaphylactic shock). This patient permanently discontinued the study drug due to IRR during the infusion at Core Cycle 4.

Adverse events

The overall safety experience in the randomised controlled studies with CT-P10 in RA is presented. Studies CT-P10 1.1 (and its maintenance Study CT-P10 1.3) and CT-P10 3.2 have shared the same inclusion/exclusion criteria for the selection of study population and study design, thus the pooled analyses have been prepared to allow review of safety across the RA population.

Table 29: Overview of Safety Experience in the CT-P10 Studies: Safety Population in RA

	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)

An overall summary of TEAEs in Study CT-P10 3.3 (Core Study Period) is presented for the safety population.

Treatment-emergent adverse events (TEAEs)

Study CT-P10 1.1

In patients with RA in Study CT-P10 1.1, the total number of treatment-emergent adverse events (TEAEs) was 281 in the CT-P10 and 142 in the Mabthera group. The randomization allocation ratio 2:1 resulted in a significantly greater number of exposed patients in CT-P10 group compared to Mabthera group. TEAEs were reported for a total of 116 (75.8%) patients; 73 [71.6%] and 43 [84.3%] in the CT-P10 group and the Mabthera group, respectively. All TEAEs reported for ≥ 3% of patients in either treatment group are presented. The TEAEs most frequently reported in the CT-P10 arm were upper respiratory tract infection (18.6%), infusion related reaction (11.8%), and urinary tract infection (10.8%). The TEAE most frequently reported in the Mabthera arm were upper respiratory tract infection (15.7%) and dyspepsia, lower respiratory tract infection and headache (each reported in 9.8%).

The majority of TEAEs were grade 1 or grade 2 in intensity and no grade 4 TEAEs were reported. The proportion of patients who experienced at least 1 grade 3 TEAE was 14 (13.7%) patients and 10 (19.6%) patients in the CT-P10 and Mabthera groups, respectively. The most frequently reported grade 3 TEAEs reported by patients was gamma-glutamyltransferase increased (2.0%) in the CT-P10 group and intervertebral disc disorder (3.9%) in the Mabthera group. No other grade 3 or higher TEAEs were reported for more than 1 patient in either treatment group.

Table 30: Summary of TEAEs in Study CT-P10 1.1: Safety Population

	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
Total number of TEAEs	281	142	423
Number (%) of patients with at least 1 TEAE	73 (71.6)	43 (84.3)	116 (75.8)
Related	46 (45.1)	31 (60.8)	77 (50.3)
Unrelated	56 (54.9)	30 (58.8)	86 (56.2)
Total number of TESAEs	17	8	25
Number (%) of patients with at least 1 TESAE	14 (13.7)	7 (13.7)	21 (13.7)
Total number of TEAEs leading to permanent study drug discontinuation	7	7	14
Number (%) of patients with at least 1 TEAE leading to permanent study drug discontinuation	6 (5.9)	4 (7.8)	10 (6.5)
Total number of TEAEs due to infection	70	35	105
Number (%) of patients with at least 1 TEAE due to infection	39 (38.2)	21 (41.2)	60 (39.2)
Total number of TEAEs due to hypersensitivity or infusion-related reactions	27	15	42
Number (%) of patients with at least 1 TEAE due to hypersensitivity or infusion-related reactions	20 (19.6)	10 (19.6)	30 (19.6)
Total number of TEAEs classed as malignancies	0	1	1
Number (%) of patients with at least 1 TEAE classed as malignancies or lymphoma	0	1 (2.0)	1 (0.7)

Note: The total number of TEAEs count includes all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
The event was considered to be related if the relationship was defined as “possible,” “probable,” or “definite.”
TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event
AE = any untoward medical occurrence in a patient enrolled (i.e., when the informed consent form [ICF] was signed) into this study regardless of its causal relationship to study drug.
TEAE = any event not present before exposure to study drug or any event already present that worsened in either intensity or frequency after exposure to study drug.
SAE (or TESAE) = any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

Table 31: Summary of TEAEs (Reported more than 3 % of Patients by PT in Either Treatment Group) in Study CT-P10 1.1: Safety Population

System Organ Class Preferred Term	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
	Number (%) of Patients		
Number (%) of patients with ≥ 1 TEAE	73 (71.6)	43 (84.3)	116 (75.8)
Blood Lymphatic system disorders	**5 (4.9)**	**7 (13.7)**	**12 (7.8)**
Anaemia	2 (2.0)	2 (3.9)	4 (2.6)
Lymphopenia	0	2 (3.9)	2 (1.3)
Neutropenia	2 (2.0)	2 (3.9)	4 (2.6)
Ear and labyrinth disorders	**0**	**3 (5.9)**	**3 (2.0)**
Tinnitus	0	2 (3.9)	2 (1.3)
Gastrointestinal disorders	**18 (17.6)**	**9 (17.6)**	**27 (17.6)**
Abdominal pain	4 (3.9)	1 (2.0)	5 (3.3)
Dyspepsia	1 (1.0)	5 (9.8)	6 (3.9)
Nausea	6 (5.9)	0	6 (3.9)
Vomiting	5 (4.9)	0	5 (3.3)
General disorders and administration site conditions	**10 (9.8)**	**4 (7.8)**	**14 (9.2)**
Pyrexia	5 (4.9)	0	5 (3.3)
Immune system disorders	**2 (2.0)**	**2 (3.9)**	**4 (2.6)**
Hypersensitivity	0	2 (3.9)	2 (1.3)
Infections and infestations	**39 (38.2)**	**21 (41.2)**	**60 (39.2)**
Herpes virus infection	3 (2.9)	4 (7.8)	7 (4.6)
Lower respiratory tract infection	7 (6.9)	5 (9.8)	12 (7.8)
Pneumonia	1 (1.0)	2 (3.9)	3 (2.0)
Rhinitis	3 (2.9)	2 (3.9)	5 (3.3)
Upper respiratory tract infection	19 (18.6)	8 (15.7)	27 (17.6)

Table 32: Summary of TEAEs (Reported more than 3% of Patients by PT in Either Treatment Group) in Study CT-P10 1.1: Safety Population (cont.)

System Organ Class Preferred Term	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
	Number (%) of Patients		
Urinary tract infection	11 (10.8)	4 (7.8)	15 (9.8)
Injury, poisoning, and procedural complications	**16 (15.7)**	**6 (11.8)**	**22 (14.4)**
Infusion related reaction	12 (11.8)	3 (5.9)	15 (9.8)
Injury	4 (3.9)	1 (2.0)	5 (3.3)
Investigations	**10 (9.8)**	**5 (9.8)**	**15 (9.8)**
Gamma-glutamyl transferase increased	4 (3.9)	1 (2.0)	5 (3.3)
Metabolism and nutrition disorders	**8 (7.8)**	**5 (9.8)**	**13 (8.5)**
Hypercholesterolaemia	4 (3.9)	1 (2.0)	5 (3.3)
Hypokalaemia	0	2 (3.9)	2 (1.3)
Musculoskeletal and connective tissue disorders	**10 (9.8)**	**9 (17.6)**	**19 (12.4)**
Back pain	2 (2.0)	2 (3.9)	4 (2.6)
Intervertebral disc disorder	1 (1.0)	2 (3.9)	3 (2.0)
Rheumatoid arthritis	4 (3.9)	0	4 (2.6)
Spinal osteoarthritis	0	2 (3.9)	2 (1.3)
Spinal pain	0	2 (3.9)	2 (1.3)
Nervous system disorders	**12 (11.8)**	**9 (17.6)**	**21 (13.7)**
Dizziness	9 (8.8)	0	9 (5.9)
Headache	6 (5.9)	5 (9.8)	11 (7.2)
Psychiatric disorders	**2 (2.0)**	**5 (9.8)**	**7 (4.6)**
Insomnia	2 (2.0)	2 (3.9)	4 (2.6)
Respiratory, thoracic and mediastinal disorders	**9 (8.8)**	**7 (13.7)**	**16 (10.5)**
Cough	2 (2.0)	3 (5.9)	5 (3.3)
Throat irritation	1 (1.0)	2 (3.9)	3 (2.0)
Skin and subcutaneous tissue disorders	**10 (9.8)**	**6 (11.8)**	**16 (10.5)**
Dermatitis	3 (2.9)	3 (5.9)	6 (3.9)
Vascular disorders	**10 (9.8)**	**6 (11.8)**	**16 (10.5)**
Hypertension	4 (3.9)	4 (7.8)	8 (5.2)

Note: Some Preferred Terms (PTs) were combined.

Study CT-P10 1.3 (Maintenance Study of CT-P10 1.1)

In patients with RA in Study CT-P10 1.3, the patients who received study drug in Maintenance Study Period were 9/38 (23.7%) patients in the CT-P10 maintenance group and 4/20 (20.0%) patients in the CT-P10 switch group experienced at least 1 TEAE. All TEAEs reported for ≥ 3% of patientswho received study drug in the Maintenance Study Period in either treatment group are summarized. TEAEs considered by the investigator to be related to study drug were reported for 2 (5.3%) patients and 2 (10.0%) patients in the CT-P10 maintenance group and CT-P10 switched group, respectively. The most frequently reported TEAEs in CT-P10 maintenance group were upper respiratory tract infection and urinary tract infection (each reported in 2 [5.3%]). In CT-P10 switch group, there was no TEAEs reported in more than 1 patient. The majority of TEAEs were grade 1 or grade 2 in intensity and no grade 4 TEAEs were reported. In Study CT-P10 1.3, 1 patient in the CT-P10 maintenance group experienced grade 3 hypertension and 1 patient in the CT-P10 switch group experienced grade 3 spinal

osteoarthritis. Both TEAEs were considered unrelated to study treatment by investigator. No other grade 3 or higher TEAEs were reported.

Table 33: Summary of TEAEs in Study CT-P10 1.3: Safety Population (Patients who Received Study Drug in Maintenance Study Period)

	CT-P10 Maintenance (N=38)	CT-P10 Switch (N=20)	Total (N=58)
Total number of TEAEs	25	7	32
Number (%) of patients with at least 1 TEAE	9 (23.7)	4 (20.0)	13 (22.4)
Related	2 (5.3)	2 (10.0)	4 (6.9)
Unrelated	9 (23.7)	3 (15.0)	12 (20.7)
Total number of TESAEs	1	1	2
Number (%) of patients with at least 1 TESAE	1 (2.6)	1 (5.0)	2 (3.4)
Total number of TEAEs leading to permanent study drug discontinuation	0	0	0
Number (%) of patients with at least 1 TEAE leading to permanent study drug discontinuation	0	0	0
Total number of TEAEs due to infection	6	2	8
Number (%) of patients with at least 1 TEAE due to infection	3 (7.9)	2 (10.0)	5 (8.6)
Total number of TEAEs due to hypersensitivity or infusion-related reactions	1	1	2
Number (%) of patients with at least 1 TEAE due to hypersensitivity or infusion-related reactions	1 (2.6)	1 (5.0)	2 (3.4)
Total number of TEAEs classed as malignancies	0	0	0

Note: The total number of TEAEs count includes all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
The event was considered to be related if the relationship was defined as “possible,” “probable,” or “definite.”
TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

Table 34: Summary of TEAEs (Reported more than 3% of Patients by PT in Either Treatment Groups) in CT-P10 1.3: Safety Population (Patients Who Received Study Drug in the Maintenance Study Period)

System Organ Class Preferred Term	CT-P10 Maintenance 1000 mg (N=38)	CT-P10 Switch 1000 mg (N=20)	Total (N=58)
	Number (%) of Patients		
Number (%) of patients with ≥ 1 TEAE	**9 (23.7)**	**4 (20.0)**	**13 (22.4)**
Blood and lymphatic system disorders	**1 (2.6)**	**1 (5.0)**	**2 (3.4)**
Neutropenia	0	1 (5.0)	1 (1.7)
Gastrointestinal disorders	**2 (5.3)**	**1 (5.0)**	**3 (5.2)**
Constipation	1 (2.6)	1 (5.0)	2 (3.4)
Infections and infestations	**3 (7.9)**	**2 (10.0)**	**5 (8.6)**
Upper respiratory tract infection	2 (5.3)	1 (5.0)	3 (5.2)
Urinary tract infection	2 (5.3)	1 (5.0)	3 (5.2)
Injury, poisoning, and procedural complications	**2 (5.3)**	**1 (5.0)**	**3 (5.2)**
Infusion-related reaction	1 (2.6)	1 (5.0)	2 (3.4)
Musculoskeletal and connective tissue disorders	**2 (5.3)**	**1 (5.0)**	**3 (5.2)**
Spinal osteoarthritis	1 (2.6)	1 (5.0)	2 (3.4)
Skin and subcutaneous tissue disorders	**1 (2.6)**	**1 (5.0)**	**2 (3.4)**
Eczema	0	1 (5.0)	1 (1.7)

Note: Some Preferred Terms (PTs) were combined.
TEAE: Treatment-emergent adverse event

Study CT-P10 3.2

In Study CT-P10 3.2, 95 (59.0%) patients in CT-P10 group, 33 (55.0%) patients in Mabthera group and 76 (50.3%) patients in Rituxan group experienced at least 1 TEAE. Of these TEAEs, the most frequently reported was infusion related reaction in CT-P10 group (25 [15.5%] patients) and Mabthera group (12 [20.0%] patients), and upper respiratory tract infection in the Rituxan group (18 [11.9%] patients). All TEAEs reported for ≥ 3% of patients in any of the 3 treatment groups are summarized.

Table 35: Summary of TEAEs (Reported more than 3% of Patients by PT in Any Treatment Group) in CT-P10 3.2 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 1000 mg (N=161)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=151)	MabThera® + Rituxan® 1000 mg (N=211)
	Number (%) of Patients			
Number (%) of patients with ≥ 1 TEAE	**95 (59.0)**	**33 (55.0)**	**76 (50.3)**	**109 (51.7)**
Blood and lymphatic system disorders	**6 (3.7)**	**3 (5.0)**	**5 (3.3)**	**8 (3.8%)**
Anaemia	3 (1.9)	2 (3.3)	4 (2.6)	6 (2.8%)
Infections and infestations	**39 (24.2)**	**11 (18.3)**	**35 (23.2)**	**46 (21.8)**
Influenza	1 (0.6)	2 (3.3)	1 (0.7)	3 (1.4)
Lower respiratory tract infection	4 (2.5)	2 (3.3)	6 (4.0)	8 (3.8)
Upper respiratory tract infection	17 (10.6)	4 (6.7)	18 (11.9)	22 (10.4)
Urinary tract infection	9 (5.6)	1 (1.7)	5 (3.3)	6 (2.8)
Injury, poisoning and procedural complications	**31 (19.3)**	**12 (20.0)**	**12 (7.9)**	**24 (11.4)**
Infusion-related reaction	25 (15.5)	12 (20.0)	8 (5.3)	20 (9.5)
Investigations	**7 (4.3)**	**3 (5.0)**	**12 (7.9)**	**15 (7.1)**
Alanine aminotransferase increased	2 (1.2)	0	5 (3.3)	5 (2.4)
Metabolism and nutrition disorders	**11 (6.8)**	**2 (3.3)**	**7 (4.6)**	**9 (4.3)**
Hypertriglyceridaemia	5 (3.1)	1 (1.7)	2 (1.3)	3 (1.4)
Nervous system disorders	**11 (6.8)**	**1 (1.7)**	**7 (4.6)**	**8 (3.8)**
Headache	5 (3.1)	1 (1.7)	5 (3.3)	6 (2.8)
Skin and subcutaneous tissue disorders	**6 (3.7)**	**2 (3.3)**	**9 (6.0)**	**11 (5.2)**
Pruritus	1 (0.6)	2 (3.3)	1 (0.7)	3 (1.4)
Vascular disorders	**8 (5.0)**	**0**	**5 (3.3)**	**5 (2.4)**
Hypertension	5 (3.1)	0	3 (2.0)	3 (1.4)

Note: Some Preferred Terms (PTs) were combined.
TEAE: Treatment-emergent adverse event

Pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2)

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), all TEAEs reported for ≥ 3% of patients in any treatment group are summarized. The proportions of patients reporting TEAEs were balanced between the treatment groups; 172 (60.8%) and 152 (58.0%) in the Total CT-P10 (CT-P10 only + Switched to CT-P10) and the reference products (Mabthera + Rituxan) groups, respectively. Of those, TEAEs considered by the investigator to be related to the study drug were reported for 97 (34.3%) patients and 90 (34.4%) patients in the Total CT-P10 (CT-P10 only + Switched to CT-P10) and the reference products groups, respectively. The majority of TEAEs were mild to moderate and their severities were similar between the 2 treatment groups. The TEAE most frequently reported was infusion related reaction and upper respiratory tract infection in the Total CT-P10and the reference products group, respectively.In addition, no TEAEs were reported for more than 1 patient in the Switched to CT-P10 group, and no notable increase in any particular SOC was observed following transition from Mabthera to CT-P10. Overall, a similar safety profile was noted across all SOCs in both treatment groups.

TESAEs were reported for 26 (9.2%) patients and 16 (6.1%) patients in the Total CT-P10 and the reference products groups, respectively. The TESAE considered by the investigator to be related to the study drugs were reported for 3 (1.1%) patients and 7 (2.7%) patients in the Total CT-P10 and the reference products groups, respectively, and there were no related TESAEs that were reported for more than 1 patient in either treatment group.

Nine patients in the each Total CTP10 and the reference products group experienced at least 1 TEAE leading to discontinuation. The most frequently reported TEAEs leading to permanent discontinuation was infusion related reaction in both Total CT-P10 and the reference products groups, which were reported for 4 patients in each treatment group.

Table 36: Summary of TEAEs (Reported more than 3% of Patients by PT in Either Treatment Group) in the Pooled Analysis for the RA Population: Safety Population

System Organ Class Preferred Term	CT-P10 only 1000 mg (N=263)	Switched to CT-P10 1000 mg (N=20)	Total CT-P10 1000 mg (N=283[1])	MabThera® + Rituxan® 1000 mg (N=262)
	Number (%) of Patients			
Number (%) of patients with ≥ 1 TEAE	**168 (63.9)**	**4 (20.0)**	**172 (60.8)**	**152 (58.0)**
Infections and infestations	**78 (29.7)**	**2 (10.0)**	**80 (28.3)**	**67 (25.6)**
Lower respiratory tract infection	11 (4.2)	0	11 (3.9)	13 (5.0)
Upper respiratory tract infection	37 (14.1)	1 (5.0)	38 (13.4)	30 (11.5)
Urinary tract infection	22 (8.4)	1 (5.0)	23 (8.1)	10 (3.8)
Injury, poisoning and procedural complications	**49 (18.6)**	**1 (5.0)**	**50 (17.7)**	**30 (11.5)**
Infusion related reaction	38 (14.4)	1 (5.0)	39 (13.8)	23 (8.8)
Gastrointestinal disorders	**30 (11.4)**	**1 (5.0)**	**31 (11.0)**	**30 (11.5)**
Abdominal pain	8 (3.0)	0	8 (2.8)	6 (2.3)
Constipation	2 (0.8)	1 (5.0)	3 (1.1)	2 (0.8)
Dyspepsia	1 (0.4)	0	1 (0.4)	8 (3.1)
Nervous system disorders	**24 (9.1)**	**0**	**24 (8.5)**	**17 (6.5)**
Dizziness	10 (3.8)	0	10 (3.5)	3 (1.1)
Headache	11 (4.2)	0	11 (3.9)	11 (4.2)
Musculoskeletal and connective tissue disorders	**22 (8.4)**	**1 (5.0)**	**23 (8.1)**	**20 (7.6)**
Spinal osteoarthritis	1 (0.4)	1 (5.0)	2 (0.7)	2 (0.8)
Vascular disorders	**19 (7.2)**	**0**	**19 (6.7)**	**11 (4.2)**
Hypertension	10 (3.8)	0	10 (3.5)	7 (2.7)
Skin and subcutaneous tissue disorders	**17 (6.5)**	**1 (5.0)**	**18 (6.4)**	**17 (6.5)**
Eczema	1 (0.4)	1 (5.0)	2 (0.7)	3 (1.1)
Blood and lymphatic system disorders	**12 (4.6)**	**1 (5.0)**	**13 (4.6)**	**15 (5.7)**
Anaemia	6 (2.3)	0	6 (2.1)	8 (3.1)
Neutropenia	2 (0.8)	1 (5.0)	3 (1.1)	3 (1.1)

Note: Some Preferred Terms (PTs) were combined. See Appendix Section 2.7.4.7.1 for further details. The su
was prepared based on the data obtained up to 104 weeks in Studies CT-P10 1.1 and CT-P10 1.3 and data
Week 24 visit in Study CT-P10 3.2. Only the most severe result was counted when a patient reported the sam
on more than 1 occasion.
[1] Safety data obtained after switching from MabThera® to CT-P10 in 20 patients (Study CT-P10 1.3) were inc
TEAE: Treatment emergent adverse event

Study CT-P10 3.3

In the AFL population (Study CT-P10 3.3), 114 (81.4%) patients experienced at least 1 TEAE; 58 (82.9%) patients and 56 (80.0%) patients in CT-P10 and Rituxan groups, respectively. The majority of TEAEs were considered by the investigator to be unrelated to the study drug. Treatment-emergent AEs considered to be related to the study drug were reported for 37 (52.9%) patients in the CT-P10 treatment group and 34 (48.6%) patients in the Rituxan treatment group. The majority of TEAEs were the CTCAE grade 1 or grade 2 in intensity.

Table 37: Summary of Tratment-Emergent Adverse Events in Study CT-P10 3.3: Safety Population

	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
Total number of TEAEs	301	319	620
Number (%) of patients with at least 1 TEAE	58 (82.9)	56 (80.0)	114 (81.4)
Related to the study drug	37 (52.9)	34 (48.6)	71 (50.7)
Unrelated to the study drug	49 (70.0)	52 (74.3)	101 (72.1)
Total number of TESAEs	29	11	40
Number (%) of patients with at least 1 TESAE	16 (22.9)	9 (12.9)	25 (17.9)
Related to the study drug	6 (8.6)	4 (5.7)	10 (7.1)
Unrelated to the study drug	11 (15.7)	6 (8.6)	17 (12.1)
Total number of TEAEs leading to permanent study drug discontinuation	5	1	6
Number (%) of patients with at least 1 TEAE leading to permanent study drug discontinuation	5 (7.1)	1 (1.4)	6 (4.3)
Related to the study drug	3 (4.3)	1 (1.4)	4 (2.9)
Unrelated to the study drug	2 (2.9)	0	2 (1.4)
Total number of TEAEs due to IRRs	22	21	43
Number (%) of patients with at least 1 TEAE due to IRR	16 (22.9)	17 (24.3)	33 (23.6)
Total number of TEAEs due to infection	35	37	72
Number (%) of patients with at least 1 TEAE due to infection	22 (31.4)	26 (37.1)	48 (34.3)
Total number of TEAEs due to PML	0	0	0
Number (%) of patients with at least 1 TEAE due to PML	0	0	0
Total number of TEAEs of malignancy	0	1	1
Number (%) of patients with at least 1 TEAE of malignancy	0	1 (1.4)	1 (0.7)

Abbreviations: CVP, cyclophosphamide, vincristine, and prednisone; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; IRR, infusion-related reaction; PML, progressive multifocal leukoencephalopathy.

Note: The total number of TEAEs included all-patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. The event was considered to be related to the study drug if the relationship was defined as 'possible', 'probable', or 'definite'.

All TEAEs reported for more than 5% of the patients in either treatment group are summarized by SOC and PT for the safety population.

The most frequently reported TEAE for the patients in the CT-P10 treatment group was neutropenia (24 [34.3%] patients) followed by IRR (16 [22.9%] patients) and constipation (12 [17.1%] patients).

The most frequently reported TEAE for the patients in the Rituxan treatment group was IRR (17 [24.3%] patients) followed by neutropenia (16 [22.9%] patients), upper respiratory tract infection and neuropathy peripheral (12 [17.1%] patients each).

Table 38: Tratment-Emergent Adverse Events Reported for More Than 5% of Patients in Either Treatment Group by System Organ Class and Preferred Term: Safety Population (Core Study Period CT-P10 3.3)

System Organ Class Preferred Term	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Blood and lymphatic system disorders			
Anaemia	5 (7.1)	4 (5.7)	9 (6.4)
Neutropenia	24 (34.3)	16 (22.9)	40 (28.6)
Gastrointestinal disorders			
Abdominal pain	6 (8.6)	10 (14.3)	16 (11.4)
Constipation	12 (17.1)	9 (12.9)	21 (15.0)
Diarrhoea	4 (5.7)	5 (7.1)	9 (6.4)
Nausea	7 (10.0)	5 (7.1)	12 (8.6)
Stomatitis	1 (1.4)	4 (5.7)	5 (3.6)
General disorders and administration site conditions			
Asthenia	3 (4.3)	6 (8.6)	9 (6.4)
Fatigue	4 (5.7)	6 (8.6)	10 (7.1)
Pyrexia	2 (2.9)	6 (8.6)	8 (5.7)
Infections and infestations			
Lower respiratory tract infection	5 (7.1)	1 (1.4)	6 (4.3)
Pneumonia	5 (7.1)	1 (1.4)	6 (4.3)
Upper respiratory tract infection	5 (7.1)	12 (17.1)	17 (12.1)
Urinary tract infection	4 (5.7)	4 (5.7)	8 (5.7)
Injury, poisoning and procedural complications			
Infusion-related reaction	16 (22.9)	17 (24.3)	33 (23.6)
Metabolism and nutrition disorders			
Decreased appetite	0	6 (8.6)	6 (4.3)
Hyperglycaemia	0	5 (7.1)	5 (3.6)
Musculoskeletal and connective tissue disorders			
Arthralgia	4 (5.7)	4 (5.7)	8 (5.7)
Back pain	1 (1.4)	7 (10.0)	8 (5.7)
Myalgia	4 (5.7)	2 (2.9)	6 (4.3)
Nervous system disorders			
Hypoaesthesia	5 (7.1)	0	5 (3.6)
Neuropathy peripheral	10 (14.3)	12 (17.1)	22 (15.7)
Paraesthesia	3 (4.3)	8 (11.4)	11 (7.9)
Psychiatric disorders			
Insomnia	0	6 (8.6)	6 (4.3)
Skin and subcutaneous tissue disorders			
Alopecia	10 (14.3)	5 (7.1)	15 (10.7)

Note: The total number of TEAEs included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events.
Medical Dictionary for Regulatory Activities Version 18.1 was used. Combined preferred term was applied.

All TEAEs considered by the investigator to be related to the study drug and reported for more than 5% of the patients in either treatment group are summarized by SOC and PT for the safety population.

Table 39: Treatment-Emergent Adverse Events Considered by the Investigator to be Related to the Study Drug Reported for More Than 5% of Patients in Either Treatment Group by System Organ Class and Preferred Term: Safety Population (Core Study Period CT-P10 3.3)

System Organ Class Preferred Term	CT-P10 (N=70) Number(%) of Patients	Rituxan (N=70)	Total (N=140)
Blood and lymphatic system disorders			
Neutropenia	15 (21.4)	5 (7.1)	20 (14.3)
General disorders and administration site conditions			
Asthenia	2 (2.9)	4 (5.7)	6 (4.3)
Fatigue	1 (1.4)	4 (5.7)	5 (3.6)
Injury, poisoning and procedural complications			
Infusion-related reaction	15 (21.4)	17 (24.3)	32 (22.9)

Note: At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted. The event was considered to be related to the study drug if the relationship was defined as 'possible', 'probable' or 'definite'.
Medical Dictionary for Regulatory Activities Version 18.1 was used. Combined preferred term was applied.

The proportion of patients who experienced at least 1 TEAE considered by the investigator to be related to the study drug was similar in the 2 treatment groups (37 [52.9%] patients and 34 [48.6%] patients in the CT-P10 and Rituxan treatment groups, respectively).

The most frequently reported TEAEs considered by the investigator to be related to the study drug were neutropenia and IRR (15 [21.4%] patients each) in the CT-P10 treatment group and IRR (17 [24.3%] patients) followed by neutropenia (5 [7.1%] patients) in the Rituxan treatment group.

The majority of TEAEs were the CTCAE grade 1 or grade 2 in intensity.

The number of patients who experienced at least 1 grade 4 TEAE considered to be related to the study drug was 4 (5.7%) patients in each treatment group. The reported grade 4 TEAEs considered to be related to the study drug were neutropenia (4 [5.7%] patients in the CT-P10 treatment group and 3 [4.3%] patients in the Rituxan treatment group) and ileus (1 [1.4%] patient in the Rituxan treatment group). The only reported grade 5 TEAE was tumour lysis syndrome which was considered to be related to the study drug (1 [1.4%] patient in the CTP10 treatment group).

The number of patients with TEAE of neutropenia was 24 (34.3%) patients and 16 (22.9%) patients in the CT-P10 and Rituxan treatment groups, respectively, and the number of patients with CTCAE grade 3 or higher of neutrophil counts decreased by the laboratory test was similar between the 2 treatment groups (19 [27.1%] patients and 14 [20.0%] patients in the CT-P10 and Rituxan treatment groups, respectively). In addition, the number (%) of patients who experienced at least 1 TEAE of febrile neutropenia was 2 (2.9%) patients in both treatment groups.

Of note, more patients in the CT-P10 treatment group had bone marrow involvement at baseline (45 [64.3%] patients in the CT-P10 treatment group and 33 [47.1%] patients in the Rituxan treatment group) and among the patients with TEAE of neutropenia, 18 patients in the CT-P10 treatment group and 7 patients in the Rituxan treatment group had bone marrow involvement at baseline.

Adverse Events of Special Interest (AESI)

In CT-P10 studies, an AESI was defined as an event that was infusion-related or was an infection, malignancy and/or progressive multifocal leukoencephalopathy (PML).

The CT-P10 safety database was screened for all AESIs highlighted as potential and identified risks of Mabthera. Some of the risks identified with Mabthera were recorded in few cases only or never occurred in the CT-P10

clinical programme. Amongst these risks, there were no reports of fatal infections, Stevens-Johnson syndrome (SJS) / toxic epidermal necrosis (TEN), acute hepatitis B infection or re-activation or HBV de novo, progressive multifocal leukoencephalopathy (PML), GI perforations, neurological disorders manifesting as posterior reversible encephalopathy syndrome (PRES). Only few AESIs belonging to other groups of risks were were reported in the Studies CT-P10 1.1 and CT-P10 1.3: acute infusion related reactions (IRRs), infections, opportunistic infections, malignancies and cardiovascular diseases and neutropenia. The safety database was systematically assessed to investigate the incidence rate of AESIs (patients with TEAEs/100PY).

Infusion-related reactions (IRRs)

Any events, signs or symptoms related to IRRs were reported as various terms by investigators. Considering the limitation of capturing these events according to the coded terms, the Applicant applied an expanded definition in the clinical development program of CT-P10 to capture all IRRs including those reported as mild and moderate in a harmonized, consistent and comprehensive manner.

For a conservative approach, 2 timeframes for IRR analysis were introduced; (i) events occurring during or within 24 hours of each infusion, (ii) events occurring within 7 days of each infusion. Both analyses captured all events irrespective of the investigator's causality assessment.

Table 40: Definition of IRRs Used in CT-P10 Studies

	Original Definition (from CSR)	New Definition #1 (Narrow Time Window)	New Definition #2 (Broad Time Window)
Terms	MedDRA PTs or Events reported as infusion related or hypersensitivity	All MedDRA PTs coded from original definition + MedDRA SMQ and additional PT from MabThera® SmPC and literatures	
Causality	Related events only	All events irrespective of the investigator's causality assessment (both related and unrelated events)	
Timeframe for IRR	Within 24 hours	Within 24 hours	Within 7 days

Note: see Appendix 2.7.4.7.3 for further details on IRR definition
CSR: Clinical safety report, IRR: infusion related reaction, MedDRA: Medical dictionary for regulatory activities, PT: Preferred term, SmPC: Summary of product characteristics, SMQ: Standardised MedDRA Queries

Studies with RA Patients: Studies CT-P10 1.1 and CT-P10 1.3

In Studies CT-P10 1.1 and CT-P10 1.3, the proportions of patients experienced at least 1 event of IRRs were similar between the treatment groups regardless of the used definition of IRRs and were not increased following transition from Mabthera to CT-P10 in Study CT-P10 1.3. The majority of IRR were reported during or following the 1st infusion of the 1st treatment course. The frequency of IRR was lower with the 2nd treatment course compared with the 1st treatment course, and lower with the 2nd infusion of study drug than with the 1st infusion within each treatment course. The numerical variations in the frequency of IRRs in the 2nd course of treatment were considered due to the small number of patients received retreatment in both treatment groups. The most frequently reported sign/symptom of IRR was headache. There were no notable differences in the reported symptom between the treatment groups.

In Study CT-P10 1.1, 20 (19.6%) patients in the CT-P10 and 10 (19.6%) patients in the Mabthera groups experienced TEAEs of IRRs. Of these, there was no case with fatal outcome, while 1 patient in CT-P10 group experienced a severe TEAE of headache and 1 patient in CT-P10 group experienced a TESAE of infusion-related reaction. Both severe and serious cases were recovered without sequelae.

The most frequently reported TEAEs of IRRs for patients in the CT-P10 group were infusion related reaction (11.8%), headache (4.9%) and dermatitis (2.0%). The most frequently reported TEAEs of IRRs for patients in the Mabthera group were infusion related reaction (5.9%) and hypersensitivity, headache and dermatitis (3.9% each). No other TEAEs of IRRs were reported for more than 1 patient in either treatment group.

In Study CT-P10 1.3, among the patients who received study drug in the Maintenance Study Period, 1 patient in each treatment group reported TEAEs of IRRs (2.6% and 5.0% in the CT-P10 maintenance and switch groups, respectively). No patients reported fatal, serious or severe IRR in Study CT-P10 1.3.

Table 41: Infusion Related Reactions: Safety Population

	RA Indication			
	Study CT-P10 1.1		Study CT-P10 1.3[1]	
	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	CT-P10 Maintenance (N=38)	CT-P10 Switch (N=20)
Total number of events	**27**	**15**	**1**	**1**
Number (%) of patients with at least 1 event	20 (19.6)	10 (19.6)	1 (2.6)	1 (5.0)
Number (%) of patients with at least 1 serious event	1 (1.0)	0	0	0
Incidence rate in patients/100 PY (95% CI for 100PY)	**18.501 (11.301, 28.573)**	**19.743 (9.468, 36.309)**	**4.755 (0.120, 26.491)**	**8.484 (0.215, 47.272)**
Severity / Nature of risk				
Grade 1	11 (10.8)	4 (7.8)	1 (2.6)	0
Grade 2	8 (7.8)	6 (11.8)	0	1 (5.0)
Grade 3	1 (1.0)	0	0	0
Outcomes				
Recovered	20 (19.6)	10 (19.6)	1 (2.6)	1 (5.0)

1Patients who received study treatment in the maintenance period.
CI: Confidence interval, PY: Patient-years, RA: Rheumatoid arthritis

Overall, most IRRs were of mild to moderate severity and no fatal cases were reported throughout Studies CT-P10 1.1 and CT-P10 1.3. Of those patients who experienced at least 1 event of IRR, 1 patient only in the CT-P10 group reported a severe (grade 3) event of headache during or following the 1st infusion of the 1st treatment course and this event was considered by the investigator as related to study drug. Severe (grade 3) events of IRRs were reported in 2 (2.0%) patients in the CT-P10 group only. While the events of acute kidney injury and hypertension were considered by the investigator to be unrelated to study drug, an event of headache were considered by the investigator to have probable relationship with study drug.

The number of patients who experienced at least 1 event of IRRs leading to the permanent study discontinuation was same throughout the definition of IRRs used and no notable differences were observed between the treatment groups. IRR leading to the permanent study discontinuation were reported for 2 (2.0 %) patients and 1 (2.0 %) patient in the CT-P10 group and Mabthera group, respectively, and these were moderate (grade 2) events of infusion related reaction reported in the CT-P10 group and moderate (grade 2) events of rash, delusion, memory impairment and mucosa vesicle reported in the Mabthera group. All these events were considered by investigator to be related to the study drug.

In addition, there were similar proportions of patients experienced at least 1 event of IRR requiring any treatment between the treatment groups in any definition of IRR used. The treatment used for IRR included antipyretics, antihistamines and glucocorticoids.

Table 42: Summary of Overall IRRs/Hypersensitivity according to the Each Definition of IRR in Studies CT-P10 1.1 and CT-P10 1.3: Safety Population

	Original Definition (from CSR)			New Definition #1 (Narrow Time Window)			New Definition #2 (Broad Time Window)		
	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Switched to CT-P10 1000 mg (N=20)	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Switched to CT-P10 1000 mg (N=20)	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Switched to CT-P10 1000 mg (N=20)
Overall									
Number of Events	28	16	1	56	25	0	69	27	1
Related	28	16	1	34	20	0	41	21	1
Unrelated	0	0	0	22	5	0	28	6	0
Number (%) of patients with ≥ 1 IRR	21 (20.6)	10 (19.6)	1 (5.0)	31 (30.4)	13 (25.5)	0	32 (31.4)	14 (27.5)	1 (5.0)
Grade 1 (mild)	12 (11.8)	4 (7.8)	0	19 (18.6)	5 (9.8)	0	19 (18.6)	6 (11.8)	0
Grade 2 (moderate)	8 (7.8)	6 (11.8)	1 (5.0)	10 (9.8)	8 (15.7)	0	11 (10.8)	8 (15.7)	1 (5.0)
Grade 3 (severe)	1 (1.0)	0	0	2 (2.0)	0	0	2 (2.0)	0	0
Number (%) of patients with ≥ 1 serious IRR	1 (1.0)	0	0	1 (1.0)	0	0	2 (2.0)	0	0
Number (%) of patients with ≥ 1 IRR leading to the discontinuation	2 (2.0)	1 (2.0)	0	2 (2.0)	1 (2.0)	0	2 (2.0)	1 (2.0)	0
Number (%) of patients with ≥ 1 IRR requiring any treatment	10 (9.8)	6 (11.8)	1 (5.0)	16 (15.7)	8 (15.7)	0	17 (16.7)	9 (17.6)	1 (5.0)

IRR: Infusion related reaction

Studies with RA Patients: Study CT-P10 3.2

In Study CT-P10 3.2, a lower proportion of patients with at least 1 event of IRRs in the Rituxan group was noted, whereas results in other treatment groups were generally similar. To understand this finding, additional analyses for IRRs were carried out with regards to the use of premedication and ADA status and no clinically meaningful differences were observed between the treatment groups or between any type of premedication and the occurrence of IRR due to the limited number of patients who did not receive premedication.

In the sensitivity analysis of Part 1 of Study CT-P10 3.2 (up to Week 24), regardless of the IRR capture algorithm used (Table 1), a higher incidence of IRRs in the Mabthera group was noted compared to other treatment groups.

Table 1: Definition of IRRs Used in CT-P10 Studies

	Original Definition (from CSR)	New Definition #1 (Narrow Time Window)	New Definition #2 (Broad Time Window)
Terms	MedDRA PTs or Events reported as infusion related or hypersensitivity	All MedDRA PTs coded from original definition + MedDRA SMQ and additional PT from MabThera® SmPC and literatures	
Causality	Related events only	All events irrespective of the investigator's causality assessment (both related and unrelated events)	
Timeframe for IRR	Within 24 hours	Within 24 hours	Within 7 days

CSR: Clinical safety report, IRR: infusion related reaction, MedDRA: Medical dictionary for regulatory activities, PT: Preferred term, SmPC: Summary of product characteristics, SMQ: Standardised MedDRA Query

In Part 1 of Study CT-P10 3.2 up to Week 48 (Table 2), and in line with findings up to Week 24, a higher incidence of IRRs in the Mabthera group was observed whereas other treatment groups were generally similar.

Table 2: Summary of IRRs/Hypersensitivity according to the Each Definition of IRRs in Study CT-P10 3.2 (Part 1) up to Week 48: Safety Population

	Original Definition (from CSR)			New Definition #1 (Narrow Window)			New Definition #2 (Broad Window)		
	CT-P10 1000 mg (N=64)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=65)	CT-P10 1000 mg (N=64)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=65)	CT-P10 1000 mg (N=64)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=65)
Overall number of events	9	15	7	14	18	13	17	22	16
Related	9	15	7	11	16	10	12	19	12
Unrelated	0	0	0	3	2	3	5	3	4
Number (%) of patients with ≥ 1 IRR	9 (14.1)	13 (21.7)	6 (9.2)	11 (17.2)	15 (25.0)	10 (15.4)	13 (20.3)	17 (28.3)	11 (16.9)
Grade 1 (mild)	2 (3.1)	6 (10.0)	2 (3.1)	4 (6.3)	7 (11.7)	3 (4.6)	6 (9.4)	9 (15.0)	4 (6.2)
Grade 2 (moderate)	5 (7.8)	7 (11.7)	4 (6.2)	5 (7.8)	8 (13.3)	7 (10.8)	5 (7.8)	8 (13.3)	7 (10.8)
Grade 3 (severe)	2 (3.1)	0	0	2 (3.1)	0	0	2 (3.1)	0	0
Number (%) of patients with ≥ 1 serious IRR	0	0	0	0	0	0	0	0	0
Number (%) of patients with ≥ 1 IRR leading to discontinuation	2 (3.1)	1 (1.7)	2 (3.1)	2 (3.1)	1 (1.7)	2 (3.1)	2 (3.1)	1 (1.7)	2 (3.1)
Number (%) of patients with ≥ 1 IRR requiring treatment	5 (7.8)	6 (10.0)	4 (6.2)	6 (9.4)	6 (10.0)	6 (9.2)	6 (9.4)	6 (10.0)	6 (9.2)

At each level of summarisation, patients were counted once if they reported 1 or more events and only the most severe event was counted. The event was considered to be related to the study drugs if the relationship was defined as 'possible', 'probable' or 'definite'.

Up to Week 48, most IRRs were of mild (grade 1) to moderate (grade 2) severity and no life-threatening (grade 4) or fatal (grade 5) cases were reported. Severe (grade 3) events of IRRs were reported in 2 patients in the CT-P10 group only during or following the 1st infusion of the 2nd treatment course (at Week 24) and recovered without sequelae.

Table 43: Summary of IRRs/Hypersensitivity According to the Each Definition of IRR in Study CT-P10 3.2 (Part 2): Safety Population

	Original Definition (from CSR)				New Definition #1 Narrow Time Window				New Definition #2 Broad Time Window			
	CT-P10 1000 mg (N=161)	MabThera 1000 mg (N=60)	Rituxan 1000 mg (N=151)	MabThera +Rituxan 1000 mg (N=211)	CT-P10 1000 mg (N=161)	MabThera 1000 mg (N=60)	Rituxan 1000 mg (N=151)	MabThera + Rituxan 1000 mg (N=211)	CT-P10 1000 mg (N=161)	MabThera 1000 mg (N=60)	Rituxan 1000 mg (N=151)	MabThera +Rituxan 1000 mg (N=211)
Overall												
No. of Events	27	13	8	21	35	14	15	29	40	18	23	41
Related	27	13	8	21	31	14	12	26	33	17	18	35
Unrelated	0	0	0	0	4	0	3	3	7	1	5	6
No. (%) of patients with ≥ 1 IRR	25 (15.5)	12 (20.0)	8 (5.3)	20 (9.5)	30 (18.6)	13 (21.7)	14 (9.3)	27 (12.8)	32 (19.9)	15 (25.0)	18 (11.9)	33 (15.6)
Grade 1	13 (8.1)	7 (11.7)	4 (2.6)	11 (5.2)	18 (11.2)	8 (13.3)	7 (4.6)	15 (7.1)	20 (12.4)	10 (16.7)	8 (5.3)	18 (8.5)
Grade 2	12 (7.5)	5 (8.3)	4 (2.6)	9 (4.3)	12 (7.5)	5 (8.3)	7 (4.6)	12 (5.7)	12 (7.5)	5 (8.3)	10 (6.6)	15 (7.1)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
No. (%) of patients with ≥ 1 serious IRR	0	0	0	0	0	0	0	0	0	0	0	0
No. (%) of patients with ≥ 1 IRR leading to discontinuation	2 (1.2)	1 (1.7)	3 (2.0)	4 (1.9)	2 (1.2)	1 (1.7)	3 (2.0)	4 (1.9)	2 (1.2)	1 (1.7)	3 (2.0)	4 (1.9)
No. (%) of patients with ≥ 1 IRR requiring treatment	11 (6.8)	5 (8.3)	4 (2.6)	9 (4.3)	14 (8.7)	5 (8.3)	6 (4.0)	11 (5.2)	15 (9.3)	5 (8.3)	10 (6.6)	15 (7.1)

IRR: Infusion related reaction, No.: number

The incidence of IRRs using new conservative definitions throughout the two treatment courses was similar for CT-P10 and Rituxan (20% and 17%, respectively) but slightly higher for MabThera (28%).

Table 44: Summary of IRRs/Hypersensitivity in CT-P10 3.3 (Part 1): Safety population

System Organ Class Preferred Term	Original Definition (from CSR)		New Definition #1 (Narrow Time Window)		New Definition #2 (Broad Time Window)	
	CT-P10 375 mg/m² (N=59)	Rituxan® 375 mg/m² (N=62)	CT-P10 375 mg/m² (N=59)	Rituxan® 375 mg/m² (N=62)	CT-P10 375 mg/m² (N=59)	Rituxan® 375 mg/m² (N=62)
Overall						
Number of Events	19	15	36	35	42	47
Related	19	15	28	20	29	25
Unrelated	0	0	8	15	13	22
Number (%) of patients with ≥ 1 IRR	15 (25.4)	13 (21.0)	22 (37.3)	20 (32.3)	24 (40.7)	23 (37.1)
Grade 1 (mild)	4 (6.8)	6 (9.7)	7 (11.9)	11 (17.7)	9 (15.3)	11 (17.7)
Grade 2 (moderate)	9 (15.3)	7 (11.3)	13 (22.0)	9 (14.5)	13 (22.0)	12 (19.4)
Grade 3 (severe)	2 (3.4)	0	2 (3.4)	0	2 (3.4)	0
Number (%) of patients with ≥ 1 serious IRR	1 (1.7)	0	1 (1.7)	0	1 (1.7)	0
Number (%) of patients with ≥ 1 IRR leading to the discontinuation	1 (1.7)	0	1 (1.7)	0	1 (1.7)	0
Number (%) of patients with ≥ 1 IRR required any treatment	12 (20.3)	12 (19.4)	17 (28.8)	17 (27.4)	19 (32.2)	18 (29.0)

IRR: Infusion related reaction

Studies with NHL Patients: Core Study Period CT-P10 3.3

Treatment-emergent AEs due to IRRs were reported for 16 (22.9%) patients and 17 (24.3%) patients in the CT-P10 and Rituxan treatment groups, respectively. The majority of TEAEs due to IRR were grade 1 or 2 in intensity. All patients received premedications of either an antipyretic (eg, paracetamol), an antihistamine (eg, H1 antihistamine) or a glucocorticoid before the infusion of CT-P10 or Rituxan over the Core Study Period. All TEAEs of IRR were grade 1 or 2 in intensity but only 3 TEAEs of IRR were reported as grade 3 in 2 patients in the CT-P10 treatment group. There was 1 TEAE of IRR which was reported to be unrelated to the study drug but related to the combination chemotherapy in the CT-P10 treatment group.

Treatment-emergent AEs considered as IRRs were reported for 2 out of 3 (66.7%) patients in the CT-P10 treatment group and 1 out of 2 (50.0%) patients in the Rituxan treatment group those who had a positive ADA result.

Occurrence of IRRs by the ADA presence

Study CT-P10 1.1

The proportions of patients reporting IRRs were balanced between ADA positive and negative subgroups.

Table 45: Summary of TEAEs Considered as Infusion Related Reactions by ADA Status at Core Week 24 in the Study CT-P10 1.1: Safety Population

	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	P-value[1]
	n/N' (%)		
ADA Positive at Core Week 24	5/18 (27.8)	2/9 (22.2)	1.000
ADA Negative at Core Week 24	12/77 (15.6)	7/37 (18.9)	0.789

1 P-value: Using Fisher's Exact test.
N' = the number of patients in each ADA positive or negative subgroup of each treatment. n = the number of patients with infusion-related reaction. (%) = n/N'*100
ADA: Anti-drug antibody

In study CT-P10 1.1, the incidences of IRRs were evaluated in the subgroup of patients by seroconversion status through 2 treatment courses and the result of analysis is presented. In the CT-P10 group, there was a slightly higher proportion of patients with IRR observed in the seroconverted subgroup while the opposite trend was noted in the Mabthera group. Overall, these new analyses using seroconversion status did not indicate a clear trend with regard to the impact of seroconversion status on IRRs.

Table 46: Summary of IRRs by Seroconversion Status in the Study CT-P10 1.1 in RA patients: Safety Population

	Original Definition (from CSR)		New Definition #1 (Narrow Window)		New Definition #2 (Broad Window)	
	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)
	n/N' (%)					
The 1st Treatment Course (Core Study Period)						
Seroconversion	11/47 (23.4)	3/25 (12.0)	13/47 (27.7)	4/25 (16.0)	15/47 (31.9)	4/25 (16.0)
Non-seroconversion	8/55 (14.5)	5/26 (19.2)	13/55 (23.6)	7/26 (26.9)	13/55 (23.6)	8/26 (30.8)
The 2nd Treatment Course (Extension Study Period)						
Seroconversion	0/12	0/5	1/12 (8.3)	0/5	1/12 (8.3)	0/5
Non-seroconversion	2/48 (4.2)	2/18 (11.1)	4/48 (8.3)	3/18 (16.7)	5/48 (10.4)	3/18 (16.7)

Note: Patients were defined as having seroconverted if the ADA test outcome changes from 'Negative' to 'Positive' during the each treatment course. All remaining patients with at least 1 ADA test outcome were included in the 'Non-seroconversion' subgroup. Percentages were calculated using the number of patients in subgroup of each treatment groups as the denominator (N') and the number of patients with the event (IRR) as the numerator (n).

Table 47: Incidence of IRRs by ADA status at Week 24 in the Study CT-P10 3.2: Safety Population

	CT-P10 1000 mg (N=161)	MabThera 1000 mg (N=60)	Rituxan 1000 mg (N=151)	MabThera +Rituxan 1000 mg (N=211)
	n/N' (%)			
Original Definition (from CSR)				
ADA positive at Week 24	4/24 (16.7)	3/16 (18.8)	0/33	3/49 (6.1)
ADA negative at Week 24	18/121 (14.9)	8/42 (19.0)	5/108 (4.6)	13/150 (8.7)
Missing	3/16 (18.8)	1/2 (50.0)	3/10 (30.0)	4/12 (33.3)
New Definition #1 (Narrow Window)				
ADA positive at Week 24	5/24 (20.8)	4/16 (25.0)	2/33 (6.1)	6/49 (12.2)
ADA negative at Week 24	21/121 (17.4)	8/42 (19.0)	9/108 (8.3)	17/150 (11.3)
Missing	4/16 (25.0)	1/2 (50.0)	3/10 (30.0)	4/12 (33.3)
New Definition #2 (Broad Window)				
ADA positive at Week 24	5/24 (20.8)	4/16 (25.0)	4/33 (12.1)	8/49 (16.3)
ADA negative at Week 24	23/121 (19.0)	10/42 (23.8)	11/108 (10.2)	21/150 (14.0)
Missing	4/16 (25.0)	1/2 (50.0)	3/10 (30.0)	4/12 (33.3)

Note: Patients who have a "Positive" result for ADA tests at Week 24 were considered as positive subgroup. Patients who have a "Negative" result for ADA tests at Week 24 were considered as negative subgroup. Patients with no immunogenicity assessment at Week 24 were included in the missing. The number of patients who were positive, negative or missing was used as the denominator (N') and the number of patients with at least 1 event of IRR up to Week 24 was used as the numerator (n).

In Study CT-P10 3.2, the ADA positive subgroup was defined as patients who developed ADA to rituximab at Week 24 regardless of immunogenicity status of Week 0 (pre-dose). The incidences of IRRs by ADA positive or negative subgroup were generally comparable between the CT-P10 and Mabthera groups with a slightly lower rate in the Rituxan group®. Within the each treatment group, the IRRs were reported with similar proportion between the ADA positive and negative subgroups. There was no consistent trend observed in all treatment groups across the analysis result. In conclusion, the analyses of IRRs by ADA status in Study CT-P10 3.2 did not

indicate any clinically significant differences between treatment groups or clear correlation between the occurrence of IRRs and ADA status.

Study CT-P10 3.3

In Study CT-P10 3.3 (Part 1), the ADA positive subgroup was defined as patients who developed ADA at any time after the 1st study drug infusion. A small number of patients were included in ADA positive subgroup; 3 (5.1%) patients and 2 (3.2%) patients in the CT-P10 and Rituxan groups, respectively. However, the proportions of patient with IRR by ADA status were similar between the treatment groups.

Table 48: Summary of IRRs by ADA status in the Study CT-P10 3.3: Safety Population

	Original Definition (from CSR)		New Definition #1 (Narrow Window)		New Definition #2 (Broad Window)	
	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)
	n/N' (%)					
ADA positive	2/3 (66.7)	1/2 (50.0)	2/3 (66.7)	1/2 (50.0)	2/3 (66.7)	1/2 (50.0)
ADA negative	10/51 (19.6)	11/55 (20.0)	16/51 (31.4)	18/55 (32.7)	18/51 (35.3)	21/55 (38.2)
Missing	3/5 (60.0)	1/5 (20.0)	4/5 (80.0)	1/5 (20.0)	4/5 (80.0)	1/5 (20.0)

Note: Patients who have at least 1 ADA positive result after study drug exposure including Core Cycle 4, unscheduled visit and end of treatment (EOT) visit were considered as ADA positive subgroup. Patient who did not have any ADA result after study drug exposure were considered as ADA missing subgroup. All other patients with ADA negative results only at post-treatment visit were considered as ADA negative subgroup. The number of patients in the each subgroup of ADA positive, negative or missing in each treatment group was used as denominator (N'). The number of patients with the event of IRRs among the patients in the each ADA subgroup was used as the numerator (n).

The majority of patients had negative results for ADA test during the Core Study Period (CT-PT 3.3).The proportion of patients with positive ADA results was similar in the 2 treatment groups during the Core Study Period. Positive ADA results at screening were reported for 13 patients (5 [7.1%] patients and 8 [11.4%] patients in the CT-P10 and Rituxan treatment groups, respectively); however, NAb was negative for all patients. A total of 5 patients (3 [4.3%] patients and 2 [2.9%] patients in the CT-P10 and Rituxan treatment groups, respectively) had at least 1 positive result for ADA tests at posttreatment visits during the Core Study Period. Of them, 3 patients (2 [2.9%] patients and 1 [1.4%] patient in the CT-P10 and Rituxan treatment groups, respectively) were early discontinued from the study treatment and the last infusion of the study drug was at Core Cycle 4 for the 2 patients in the CT-P10 treatment group and at Core Cycle 2 for the other 1 patient in the Rituxan treatment group. Two patients (1 patient in each treatment group) received a full dose of infusion at each cycle during the Core Study Period and had positive results at Core Cycle 4 and negative results at Core Cycle 8 (EOT1). All patients with ADA positive result at posttreatment visits had positive results for NAb test with the exception of 1 patient in the CT-P10 treatment group.

Tumour Lysis Syndrome (Identified Risk in NHL/CLL Only)

Throughout the CT-P10 studies, there was 1 fatal case due to TLS reported in an AFL patient (Study CT-P10 3.3). This patient was treated with 1 cycle of CT-P10 in combination with CVP during the study period. Across all clinical studies with CT-P10, no other TLS cases have been reported to date.

Infections, Including Serious Infections

In Study CT-P10 1.1, TEAEs of infection were reported for 39 (38.2%) patients and 21 (41.2%) patients in the CT-P10 and Mabthera groups, respectively. No fatal or severe cases were reported. One patient in each arm experienced a serious infection (diverticulitis and lobar pneumonia), which recovered without sequelae. The most frequently reported TEAEs of infection for patients in both CT-P10 and Mabthera group were upper respiratory tract infection (18.6% and 15.7% patients, respectively) and urinary tract infection (11% and 8%, respectively).

In Study CT-P10 1.3, TEAEs of infection were reported for 3 (7.9%) patients and 2 (10.0%) patients in the CT-P10 maintenance and switched groups, respectively. No patients reported fatal, serious or severe infection in Study CT-P10 1.3.

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), 80 (28.3%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) group and 67 (25.6%) patients in the reference products (Mabthera + Rituxan) group reported at least 1 event of infection. The majority of events of infections were grade 1 (mild) and 2 (moderate) in severity whereas grade 3 (severe) events were reported for 2 (0.7%) patients and 4 (1.5%) patients in the Total CT-P10 and the reference products groups, respectively. These events include an unrelated event of a urinary tract infection and an unrelated event of gastroenteritis in the Total CT-P10 group and 2 related events of pneumonia, an unrelated event of bronchitis and a related event of cellulitis in the reference products group. Of those, none of events in the Total CT-P10 group and all events in the reference products group were serious. There was 1 fatal event of infection in the Total CT-P10 group which was cellulitis.

Serious events of infections were reported in 3 (1.1%) patients and 4 (1.5 %) patients in the CT-P10 and the reference products groups, respectively. In the AFL population (Core Study Period CT-P10 3.3), treatment-emergent AEs due to infection were reported for 22 (31.4%) patients and 26 (37.1%) patients in the CT-P10 and Rituxan treatment groups, respectively. The majority of TEAEs due to infection were unrelated to the study drug. The TEAEs due to infection considered to be related to the study drug were reported for 6 (8.6%) patients in the CT-P10 treatment group and 9 (12.9%) patients in the Rituxan treatment group. The most frequently reported TEAEs due to infection in the CT-P10 treatment group were lower respiratory tract infection, pneumonia and upper respiratory tract infection (5 [7.1%] patients each). The number of patients was 5 (7.1%) patients in the CT-P10 treatment group and 1 (1.4%) patient in the Rituxan treatment group for each TEAE of pneumonia and lower respiratory tract infection. In total, the number of patients with at least 1 of the respiratory infections (influenza, upper respiratory tract infection, tracheobronchitis, lower respiratory tract infection or pneumonia) was similar between the 2 treatment groups (16 [22.6%] patients in each treatment group).

The incidence rate of infections in RA and NHL patients was similar between the 2 treatment groups. There were no events of serious viral infection (Identified Risk in NHL/CLL) reported throughout the studies with CT-P10.

Table 49: Summary of Infections in All CT-P10 Studies: Safety Population

	Pooled in RA Population (CT-P10 1.1 + 1.3 + 3.2)		NHL Population (CT-P10 3.3)	
	Total CT-P10 1000 mg	MabThera® + Rituxan® 1000 mg	CT-P10 375 mg/m²	Rituxan® 375 mg/m²
	(N=283[1])	(N=262)	(N=59)	(N=62)
Total number of events	135	93	12	14
Number (%) of patients with ≥ 1 event	80 (28.3)	67 (25.6)	12 (20.3)	13 (21.0)
Number (%) of patients with ≥ 1 serious event	3 (1.1)	4 (1.5)	1 (1.7)	0
Incidence rate in patients/100 PY (95 % CI)	37.50 (29.73 – 46.67)	45.97 (35.62 – 58.38)	88.10 (45.52 – 153.89)	92.40 (49.20 – 158.00)
Severity / Nature of risk				
Grade 1 (mild)	22 (7.8)	20 (7.6)	2 (3.4)	3 (4.8)
Grade 2 (moderate)	55 (19.4)	43 (16.4)	9 (15.3)	10 (16.1)
Grade 3 (severe)	2 (0.7)	4 (1.5)	1 (1.7)	0
Grade 4 (life-threatening)	0	0	0	0
Grade 5	1 (0.4)	0	0	0
Outcomes				
Recovered	74 (26.1)	66 (25.2)	12 (20.3)	13 (21.0)
Recovering	3 (1.1)	1 (0.4)	0	0
Not recovered	2 (0.7)	0	0	0
Fatal	1 (0.4)	0	0	0

[1] Safety data obtained after switching from MabThera® to CT-P10 in 20 patients (Study CT-P10 1.3) were included.
CI: Confidence interval, NHL: Non-Hodgkin's lymphoma, RA: Rheumatoid arthritis, PY: Patient year

Opportunistic Infections

In Study CT-P10 1.1, one (1.0%) patient in CT-P10 group and 3 (5.9%) patients in Mabthera group experienced TEAEs of herpes zoster which considered as opportunistic infection. All patients recovered. No fatal, severe or serious opportunistic infections were reported in this study. In Study CT-P10 1.3, no patient experienced TEAEs considered as opportunistic infection.

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), 5 (1.8%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) group and 6 (2.3%) patients in the reference products (Mabthera + Rituxan) group reported at least 1 event of opportunistic infections. The majority of events of opportunistic infections were grade 1 (mild) and 2 (moderate) in severity and grade 3 (severe) and serious events of opportunistic infections was reported for 1 (0.4%) patient in the reference products group only; a related event of pneumocystis jirovecii pneumonia.

In the NHL population (Study CT-P10 3.3), 1 (1.7%) patients in the CT-P10 group and 2 (3.2%) patients in the Rituxan groups reported at least 1 event of opportunistic infections. No grade 3 (severe) or serious events were reported in either treatment group.

The incidence rates of opportunistic infections in RA and NHL patients were similar between the 2 treatment groups.

Table 50: Summary of Opportunistic Infections in All CT-P10 Studies: Safety Population

	Pooled in RA Population (CT-P10 1.1 + 1.3 + 3.2)		NHL Population (CT-P10 3.3)	
	Total CT-P10 1000 mg	MabThera® + Rituxan® 1000 mg	CT-P10 375 mg/m²	Rituxan® 375 mg/m²
	(N=283[1])	(N=262)	(N=59)	(N=62)
Total number of events	5	6	1	2
Number (%) of patients with at least 1 event	5 (1.8)	6 (2.3)	1 (1.7)	2 (3.2)
Number (%) of patients with at least 1 serious event	0	1 (0.4)	0	0
Incidence rate in patients/100 PY (95 % CI)	2.34 (0.76 – 5.47)	4.12 (1.51 – 8.96)	7.34 (0.19 – 40.91)	14.22 (1.72 – 51.35)
Severity / Nature of risk				
Grade 1 (mild)	1 (0.4)	3 (1.1)	0	1 (1.6)
Grade 2 (moderate)	4 (1.4)	2 (0.8)	1 (1.7)	1 (1.6)
Grade 3 (severe)	0	1 (0.4)	0	0
Outcomes				
Recovered	4 (1.4)	6 (2.3)	1 (1.7)	2 (3.2)
Not recovered	1 (0.4)	0	0	0

[1] Safety data obtained after switching from MabThera® to CT-P10 in 20 patients (Study CT-P10 1.3) were included.
CI: Confidence interval, NHL: Non-Hodgkin's lymphoma, RA: Rheumatoid arthritis, PY: Patient year

Hepatitis B Virus Reactivation

In Studies CT-P10 1.1 and CT-P10 1.3, there was 1 patient who had a positive test result in the HBV DNA test for HBsAb and HBcIg. However, it was not considered as an AE by the investigator. Throughout the CT-P10 clinical studies, no other patients experienced hepatitis B reactivation or positive HBV DNA results, including the ongoing Study CT-P10 3.3.

Malignant Events

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), patient in the reference products (Mabthera + Rituxan) group reported at least 1 event of malignancy. Grade 3 (severe) or serious events of malignancy were reported for 1 (0.4%) patient each in the CT-P10 and the reference products groups, respectively.(both from Study CT-P10 1.1: a grade 3 and serious event of cervix carcinoma stage 0 and a grade 1 and serious event of adrenal neoplasm. The event of adrenal neoplasm was originally reported by investigator as 'adrenal incidentaloma'. This event occurred 15 days after the 1st study drug infusion and assessed by the investigator as unrelated with the study drugs. Investigator also considered that this event was not malignant and with a follow-up for 1 year, it was confirmed that the both right and left adrenal gland are in normal size without abnormal hormone activity. This event was recovered with sequelae.

An additional malignant event reported for 1 patient in the Total CT-P10 group (Study CT-P10 3.2) was a grade 1 and non-serious event of thyroid neoplasm. This event was originally reported by the investigator as 'both thyroid nodule' but coded as thyroid neoplasm. Further follow up on this case will be performed until the end of study to confirm actual malignancy. All these malignant events were considered by investigator as not related to the study drugs.

One TEAE classified as malignancy was reported for 1 (1.4%) patient in the Rituxan treatment group in Core Study Period CT-P10 3.3.

Second Primary Malignancy

In Study CT-P10 3.3, there was 1 event of secondary malignancy reported for 1 patient in the Rituxan group and considered to be unrelated to the study drug by investigator. This patient experienced the grade 3 (severe) event of basal cell carcinoma.

Neutropenia

TEAEs of neutropenia and leukopenia were reported in 3 (2.9%) patients in CT-P10 group and 2 (3.9%) patients in Mabthera group in Study CT-P10 1.1. All events were considered by the investigator to be related to the study drug. Of those, only 1 patient in Mabthera group experienced a severe and serious TEAE of neutropenia and discontinued the study permanently. No other severe or fatal case of neutropenia was reported. CTCAE grade 4 decreased total neutrophil counts were reported in 2 (2.0%) patients and 3 (5.9%) patients in CT-P10 and Mabthera groups, respectively. Except 1 patient from each treatment group, these CTCAE grade 4 were not considered as TEAEs in the opinion of the investigators. In Study CT-P10 1.3, 1 (5.0%) patient in the CT-P10 switch group reported TEAE of neutropenia and recovered without sequelae and this patient had no TEAE of infections. No fatal, severe or serious neutropenia was reported in this study.

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), there was similar proportions of patients with neutropenia between the treatment groups; 5 (1.8%) patients and 3 (1.1%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) and the reference products (Mabthera + Rituxan) groups, respectively. Of those, serious and nonserious grade 3 (severe) events were reported in 1 (0.4%) patient in the reference products group only.

In the NHL population (Study CT-P10 3.3), a slightly higher proportion of patients with neutropenia in the CT-P10 group was noted; 13 (22.0%) and 9 (14.5%) patients in the CT-P10 group and Rituxan group, respectively. However, there were no notable differences between the treatment groups with regard to the severe (grade 3) or life-threatening (grade 4) events of neutropenia; 10 (16.9%) patient and 8 (12.9%) patients in the CT-P10 and Rituxan group, respectively. Serious events were reported for 1 patient in each treatment groups.

Table 51: Summary of Neutropenia in All CT-P10 Studies: Safety Population

	Pooled in RA Population (CT-P10 1.1 + 1.3 + 3.2)		NHL Population (CT-P10 3.3)	
	CT-P10 1000 mg	MabThera® + Rituxan® 1000 mg	CT-P10 375 mg/m²	Rituxan® 375 mg/m²
	(N=283[1])	(N=262)	(N=59)	(N=62)
Total number of events	5	3	21	12
Number (%) of patients with at least 1 event	5 (1.8)	3 (1.1)	13 (22.0)	9 (14.5)
Number (%) of patients with at least 1 serious event	0	1 (0.4)	1 (1.7)	1 (1.6)
Incidence rate in patients/100 PY (95 % CI)	2.34 (0.76 – 5.47)	2.06 (0.42 – 6.02)	95.4 (50.82 – 163.21)	64.0 (29.25 – 121.43)
Severity / Nature of risk				
Grade 1 (mild)	5 (1.8)	2 (0.8)	1 (1.7)	0
Grade 2 (moderate)	0	0	2 (3.4)	1 (1.6)
Grade 3 (severe)	0	1 (0.4)	9 (15.3)	4 (6.5)
Grade 4 (life-threatening)	0	0	1 (1.7)	4 (6.5)
Outcomes				
Recovered	5 (1.8)	3 (1.1)	12 (20.3)	9 (14.5)
Not recovered	0	0	1 (1.7)	0

[1] Safety data obtained after switching from MabThera® to CT-P10 in 20 patients (Study CT-P10 1.3) were included.
CI: Confidence interval, NHL: Non-Hodgkin's lymphoma, RA: Rheumatoid arthritis, PY: Patient-years

Prolonged B-cell Depletion

The longest exposure in the clinical studies with CT-P10 covers a period up to 104 weeks (Study CT-P10 1.3). The proportion of patients with B cell depletion was similar between CT-P10 and Mabthera groups throughout the study. All patients who received study drug in CT-P10studies were followed up until recovery of B-cell or IgM (equal to or higher than the LLN or atleast 50% of the baseline value).

Impact on Cardiovascular Disease

In Study CT-P10 1.1, 14.7% patients in the CT-P10 group and 13.7% in the Mabthera group experienced TEAEs of cardiovascular nature. Of those, 1 patient reported a severe and non-serious TEAE of hypertension, and 4 (3.9%) patients reported severe and serious events; deep vein thrombosis, mitral valve prolapse, pericardial effusion and arrhythmia. All cases were reported in CT-P10 group and recovered without sequelae. In Study CT-P10 1.3, 1 (2.6%) patient in the CT-P10 Maintenance group experienced a severe TEAE of hypertension which was ongoing from Study CT-P10 1.1.

When pooled across CT-P10 studies conducted in RA patients (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), the proportion of patients at least 1 event of cardiovascular disease were 25 (8.8%) patient and 14 (5.3%) patients in the Total CT-P10 group (CT-P10 + Switched to CTP10) and the reference products (Mabthera + Rituxan) group, respectively. Of those, events considered by the investigator to be related to the study drug were reported for 3 (1.1%) patients and 5 (1.9%) patients in the Total CT-P10 group and the reference products group, respectively.

There were 6 serious cardiovascular events reported for each 1 patient in the CT-P10 group only (6 [2.1%] patients), but all these events were considered by investigator to be unrelated to the study drug.

In the pooled analysis for the RA population (Study CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), a higher proportion of patients have at least 1 risk factor for cardiovascular disease in the Total CT-P10 group; 158 (55.8%) patients and 128 (48.9%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) group and the reference products (Mabthera + Rituxan) group, respectively. Among those patients without any risk factors for cardiovascular disease, the proportion of patients experienced cardiovascular events were similar with 5 (4.0%) patients and 5 (3.7%) patients in the Total CT-P10 group and the reference products group, respectively. Similar proportions of patients reported cardiovascular events in Study CT-P10 3.3 in AFL patients; 2 (3.4%) patients and 4 (6.5%) in the CT-P10 and Rituxan groups, respectively with a slightly lower rates in the CT-P10 group.

Hypogammaglobulinaemia

In Study CT-P10 1.1, mean changes from baseline in IgM, IgG, and IgA were small, and there were no notable differences between the 2 treatment groups.

The dataset of Study CT-P10 1.3 was relatively small but there were no notable differences in the mean change from baseline in immunoglobulin level between treatment groups

Up to Main Week 24 in Study CT-P10 3.2 and Core Cycle 4 (12 weeks) in Study CT-P10 3.3, mean changes from baseline in IgM, IgG, and IgA were small at each time point, and there were no notable differences between treatment groups.

Other Observations Related to Safety

Grade 3 or 4 and Serious Blood and Lymphatic System AEs in Patients > 70 years (Potential Risk in NHL/CLL): In the CT-P10 AFL study (CT-P10 3.3), of those patients > 70 years of age, 1 patient (1.6%) experienced grade

3 and serious events of leukopenia in the Rituxan group only. This event was considered by investigator to be related to study drug as well as cyclophosphamide.

Interferon-γ Release Assay (Study CT-P10 1.1 Only): Fourteen patients (13.7%) and 2 patients (2.0%) in the CT-P10 group and 5 patients (9.8%) and 2 patients (3.9%) in the Mabthera group had positive IFN-γ results at Screening and during the Core Study Period, respectively. One (2.0%) patient in the Mabthera group had an indeterminate IFN-γ result at Screening. One (1.0%) patient in the CT-P10 group had an indeterminate IFN-γ result during the Core Study Period.

Chest X-ray for TB Assessment: In Study CT-P10 1.1, the majority of patients had normal chest x-rays at each time point. No positive TB results were reported for patients in either treatment groups at any time point in the Core or Extension Study Period. One patient in the Mabthera group reported an abnormal, clinically significant chest x-ray at Week 24 of the Core Study Period; vascular markings on the lung. One patients in the CT-P10 group reported compaction of lung parenchyma and atherosclerotic aorta at Week 0 of the Extension Study Period.In Study CT-P10 1.3, no abnormal, clinically significant chest x-ray results reported at any time point.

Impaired Immunisation Response (Identified Risk in All Indications): There were no cases of vaccine failure reported throughout the CT-P10 clinical studies.

Progressive Multifocal Leukoencephalopathy: In study CT-P10 3.3 (Core Study Period) no TEAEs due to PML were reported for patients in the CT-P10 and Rituxan treatment groups.

Tuberculosis assessment: In study CT-P10 3.3 (Core Study Period) all patients in both treatment groups had normal TB assessments at baseline with the exception of 2 (1.4%) patients who had an abnormal, not clinically significant assessment in the Rituxan treatment group. At each postbaseline visit all patients in both treatment groups had normal TB assessments except 1 patient with the result of abnormal, not clinically significant at baseline who permanently discontinued the study treatment due to reactivation of primary tuberculosis in the Rituxan treatment group.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Study CT-P10 1.1

In Study CT-P10 1.1, all reported TESAEs are summarized (table 56). A total of 21 patients reported TESAEs; 14 (13.7%) patients experiencing 17 SAEs in the CT-P10 group and 7 (13.7%) patients experiencing 8 SAEs in the Mabthera group. The distribution of TESAEs is aligned with the randomization allocation of 2:1 in the study. The TESAEs that were considered by the investigator to be related to study drug were reported for 3 (2.9%) patients and 2 (3.9%) patients in the CT-P10 and Mabthera group, respectively.

There was only 1 TESAE reported in more than 1 patient (intervertebral disc disorder, 2 [3.9%] patients in Mabthera group) and both cases were considered by the investigator to be unrelated to the study drug. No other TESAE was reported for more than 1 patient in either treatment group.

Table 52: Summary of TESAEs in Study CT-P10 1.1: Safety Population

System Organ Class Preferred Term	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
	Number (%) of Patients		
Total number of TESAEs	**17**	**8**	**25**
Number (%) of patients with ≥ 1 TESAE	**14 (13.7)**	**7 (13.7)**	**21 (13.7)**
Related	3 (2.9)	2 (3.9)	5 (3.3)
Unrelated	11 (10.8)	5 (9.8)	16 (10.5)
Blood and lymphatic system disorders	**0**	**1 (2.0)**	**1 (0.7)**
Neutropenia (related, grade 3)	0	1 (2.0)	1 (0.7)
Cardiac disorders	**3 (2.9)**	**0**	**3 (2.0)**
Arrhythmia (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Mitral valve prolapse (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Pericardial effusion (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Eye disorders	**2 (2.0)**	**0**	**2 (1.3)**
Ocular retrobulbar haemorrhage (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Uveitis (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Gastrointestinal disorders	**0**	**1 (2.0)**	**1 (0.7)**
Irritable bowel syndrome (unrelated, grade 3)	0	1 (2.0)	1 (0.7)
Infections and infestations	**1 (1.0)**	**1 (2.0)**	**2 (1.3)**
Diverticulitis (unrelated, grade 1)	1 (1.0)	0	1 (0.7)
Pneumonia (related, grade 3)	0	1 (2.0)	1 (0.7)
Injury, poisoning and procedural complications	**2 (2.0)**	**1 (2.0)**	**3 (2.0)**
Fracture (unrelated, grade 3)	0	1 (2.0)	1 (0.7)
Infusion related reaction (related, grade 2)	1 (1.0)	0	1 (0.7)
Injury (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Musculoskeletal and connective tissue disorders	**4 (3.9)**	**2 (3.9)**	**6 (3.9)**
Back pain (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Intervertebral disc disorder (unrelated, grade 3)	0	2 (3.9)	2 (1.3)
Osteonecrosis (related, grade 3)	1 (1.0)	0	1 (0.7)
Rheumatoid arthritis (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Spondylolisthesis (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.0)**	**1 (2.0)**	**2 (1.3)**
Adrenal neoplasm (unrelated, grade 1)	1 (1.0)	0	1 (0.7)
Cervix carcinoma stage 0 (unrelated, grade 3)	0	1 (2.0)	1 (0.7)
Nervous system disorders	**1 (1.0)**	**1 (2.0)**	**2 (1.3)**
Cerebral infarction (unrelated, grade 2)	1 (1.0)	0	1 (0.7)
Sciatica (unrelated, grade 2)	0	1 (2.0)	1 (0.7)
Skin and subcutaneous tissue disorders	**2 (2.0)**	**0**	**2 (1.3)**
Hyperkeratosis (unrelated, grade 3)	1 (1.0)	0	1 (0.7)
Rash (related, grade 2)	1 (1.0)	0	1 (0.7)
Vascular disorders	**1 (1.0)**	**0**	**1 (0.7)**
Deep vein thrombosis (unrelated, grade 2)	1 (1.0)	0	1 (0.7)

Study CT-P10 1.3 (Maintenance Study of CT-P10 1.1)

In Study CT-P10 1.3, among patients who received study drug in the Maintenance Study Period,1 patient in each treatment group experienced a TESAE of spinal osteoarthritis. Both TEAEs were considered unrelated to study treatment by the investigator.No other TESAE were reported.

Study CT-P10 3.2

In Study CT-P10 3.2, all reported TESAEs are summarized for the safety population in table 57. A total of19 patients reported at least 1 TESAE; 10 (6.2%) patients in the CT-P10 group and 9 (6.0%) patients in the Rituxan group. No TESAE was reported in the Mabthera group. TESAEs considered to be related to the study drug were reported for 5 (3.3%) patients in the Rituxan group only. The most frequently reported TESAE in the CT-P10 group was fracture, which was reported for 2 (1.2%) patients, and no other TESAEs were reported for more than 1 patient in any of the 3 treatment groups.

Table 53: Summary of TESAEs in Study CT-P10 3.2 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 1000 mg (N=161)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=151)	MabThera® + Rituxan® (N=211)
	Number (%) of Patients			
Total number of TESAEs	**11**	**0**	**10**	**10**
Number (%) of patients with ≥ 1 TESAE	**10 (6.2)**	**0**	**9 (6.0)**	**9 (4.3)**
Related	0	0	5 (3.3)	5 (2.4)
Unrelated	10 (6.2)	0	5 (3.3)	5 (2.4)
Blood and lymphatic system disorders	**0**	**0**	**1 (0.7)**	**1 (0.5)**
Pancytopenia (related, grade 4)	0	0	1 (0.7)	1 (0.5)
Cardiac disorders	**1 (0.6)**	**0**	**0**	**0**
Myocardial ischaemia (unrelated, grade 2)	1 (0.6)	0	0	0
Gastrointestinal disorders	**0**	**0**	**1 (0.7)**	**1 (0.5)**
Intestinal obstruction (unrelated, grade 3)	0	0	1 (0.7)	1 (0.5)
General disorders and administration site conditions	**1 (0.6)**	**0**	**0**	**0**
Chest pain (unrelated, grade 2)	1 (0.6)	0	0	0
Hepatobiliary disorders	**1 (0.6)**	**0**	**0**	**0**
Bile duct stone (unrelated, grade 3)	1 (0.6)	0	0	0
Infections and infestations	**2 (1.2)**	**0**	**3 (2.0)**	**3 (1.4)**
Cellulitis (related, grade 3)	0	0	1 (0.7)	1 (0.5)
Cellulitis (unrelated, grade 5)	1 (0.6)	0	0	0
Lower respiratory tract infection (unrelated, grade 3)	0	0	1 (0.7)	1 (0.5)
Otitis (unrelated, grade 1)	1 (0.6)	0	0	0
Pneumonia (related, grade 3)	0	0	1 (0.7)	1 (0.5)
Injury, poisoning and procedural complications	**2 (1.2)**	**0**	**2 (1.3)**	**2 (0.9)**
Fracture (unrelated, grade 3)	2 (1.2)	0	1 (0.7)	1 (0.5)
Injury (unrelated, grade 3)	0	0	1 (0.7)	1 (0.5)
Musculoskeletal and connective tissue disorders	**1 (0.6)**	**0**	**1 (0.7)**	**1 (0.5)**
Arthralgia (related, grade 3)	0	0	1 (0.7)	1 (0.5)
Hand deformity (unrelated, grade 2)	1 (0.6)	0	0	0
Nervous system disorders	**1 (0.6)**	**0**	**1 (0.7)**	**1 (0.5)**
Parkinson's disease (unrelated, grade 2)	1 (0.6)	0	0	0
Vertebrobasilar insufficiency (unrelated, grade 2)	0	0	1 (0.7)	1 (0.5)
Renal and urinary disorders	**1 (0.6)**	**0**	**0**	**0**
Acute kidney injury (unrelated, grade 3)	1 (0.6)	0	0	0
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (0.7)**	**1 (0.5)**
Eczema (related, grade 2)	0	0	1 (0.7)	1 (0.5)
Vascular disorders	**1 (0.6)**	**0**	**0**	**0**
Vena cava thrombosis	1 (0.6)	0	0	0

Pooled Analysis for the RA Population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2)

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), all reported TESAEs are summarised. The types and incidences of TESAEs were similar between the Total CT-P10 (CT-P10 only + Switched to CT-P10) and the reference products (Mabthera + Rituxan) groups; 26 (9.2%) and 16 (6.1%) in the Total CT-P10 and the reference products groups, respectively. TESAEs were considered to be related to the study drug in 3 (1.1%) patients in the CT-P10 group and in 7 (2.7%) patients in the reference product group. The TESAEs reported in more than 1 patient in any treatment group were fracture and spinal osteoarthritis (2

patients (0.7 %) each) in the Total CT-P10 group and pneumonia, fracture and intervertebral disc disorder (2 (0.8%) patients each) in the reference products group. No other TEAEs were reported in more than 1 patient in either treatment group. In addition, no TESAEs were reported for more than 1 patient in the Switched to CT-P10 group, and no notable increase in any particular SOC was observed following transition from Mabthera to CT-P10.

Table 54: Summary of TESAEs in the Pooled Analysis for the RA Population: Safety Population

System Organ Class Preferred Term	CT-P10 only 1000 mg (N=263)	Switched to CT-P10 1000 mg (N=20)	Total CT-P10 1000 mg (N=283[1])	MabThera® + Rituxan® 1000 mg (N=262)
	Number (%) of Patients			
Total number of TESAEs	**29**	**1**	**30**	**18**
Number (%) of patients with ≥ 1 TESAE	**25 (9.5)**	**1 (5.0)**	**26 (9.2)**	**16 (6.1)**
Related	3 (1.1)	0	3 (1.1)	7 (2.7)
Unrelated	22 (8.4)	1 (5.0)	23 (8.1)	10 (3.8)
Blood and lymphatic system disorders	**0**	**0**	**0**	**2 (0.8)**
Neutropenia (related, grade 3)	0	0	0	1 (0.4)
Pancytopenia (related, grade 4)	0	0	0	1 (0.4)
Cardiac disorders	**4 (1.5)**	**0**	**4 (1.4)**	**0**
Arrhythmia (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Mitral valve prolapse (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Myocardial ischaemia (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Pericardial effusion (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Eye disorders	**2 (0.8)**	**0**	**2 (0.7)**	**0**
Ocular retrobulbar haemorrhage (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Uveitis (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Gastrointestinal disorders	**0**	**0**	**0**	**2 (0.8)**
Intestinal obstruction (unrelated, grade 3)	0	0	0	1 (0.4)
Irritable bowel syndrome (unrelated, grade 3)	0	0	0	1 (0.4)
General disorders and administration site conditions	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Chest pain (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Hepatobiliary disorders	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Bile duct stone (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Infections and infestations	**3 (1.1)**	**0**	**3 (1.1)**	**4 (1.5)**
Cellulitis (related, grade 3)	0	0	0	1 (0.4)
Cellulitis (unrelated, grade 5)	1 (0.4)	0	1 (0.4)	0
Diverticulitis (unrelated, grade 1)	1 (0.4)	0	1 (0.4)	0
Lower respiratory tract infection (unrelated, grade 3)	0	0	0	1 (0.4)
Otitis (unrelated, grade 1)	1 (0.4)	0	1 (0.4)	0
Pneumonia (related, grade 3)	0	0	0	2 (0.8)
Injury, poisoning and procedural complications	**4 (1.5)**	**0**	**4 (1.4)**	**3 (1.1)**
Fracture (unrelated, grade 3)	2 (0.8)	0	2 (0.7)	2 (0.8)
Infusion related reaction (related, grade 2)	1 (0.4)	0	1 (0.4)	0
Injury (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	**6 (2.3)**	**1 (5.0)**	**7 (2.5)**	**3 (1.1)**
Arthralgia (related, grade 3)	0	0	0	1 (0.4)

Table 55: Summary of TESAEs in the Pooled Analysis for the RA Population: Safety Population (cont)

System Organ Class Preferred Term	CT-P10 only 1000 mg (N=263)	Switched to CT-P10 1000 mg (N=20)	Total CT-P10 1000 mg (N=283[1])	MabThera® + Rituxan® 1000 mg (N=262)
	Number (%) of Patients			
Back pain (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Hand deformity (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Intervertebral disc disorder (unrelated, grade 3)	0	0	0	2 (0.8)
Osteonecrosis (related, grade 3)	1 (0.4)	0	1 (0.4)	0
Rheumatoid arthritis (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Spinal osteoarthritis (unrelated, grade 1)	1 (0.4)	0	1 (0.4)	0
Spinal osteoarthritis (unrelated, grade 3)	0	1 (5.0)	1 (0.4)	0
Spondylolisthesis (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4)**	**0**	**1 (0.4)**	**1 (0.4)**
Adrenal neoplasm (unrelated, grade 1)	1 (0.4)	0	1 (0.4)	0
Cervix carcinoma stage 0 (unrelated, grade 3)	0	0	0	1 (0.4)
Nervous system disorders	**2 (0.8)**	**0**	**2 (0.7)**	**2 (0.8)**
Cerebral infarction (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Parkinson's disease (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Sciatica (unrelated, grade 2)	0	0	0	1 (0.4)
Vertebrobasilar insufficiency (unrelated, grade 2)	0	0	0	1 (0.4)
Renal and urinary disorders	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Acute kidney injury (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Skin and subcutaneous tissue disorders	**2 (0.8)**	**0**	**2 (0.7)**	**1 (0.4)**
Eczema (related, grade 2)	0	0	0	1 (0.4)
Hyperkeratosis (unrelated, grade 3)	1 (0.4)	0	1 (0.4)	0
Rash (related, grade 2)	1 (0.4)	0	1 (0.4)	0
Vascular disorders	**2 (0.8)**	**0**	**2 (0.7)**	**0**
Deep vein thrombosis (unrelated, grade 2)	1 (0.4)	0	1 (0.4)	0
Vena cava thrombosis	1 (0.4)	0	1 (0.4)	0

Study CT-P10 3.3 (Core Study Period)

All TESAEs are summarized for the safety population. The number of patients who experienced at least 1 TESAE was 16 (22.9%) patients and 9 (12.9%) patients in the CT-P10 and Rituxan treatment groups, respectively. The proportion of patients who experienced at least 1 TESAE considered by the investigator to be related to the study drug was similar in the 2 treatment groups (6 [8.6%] patients and 4 [5.7%] patients in the CT-P10 and Rituxan treatment groups, respectively).

Only 1 patient had a TESAE of cardiac disorder during the Core Study Period in the CT-P10 treatment group. The event was considered by the investigator to be unrelated to the study drug but caused by underlying cardiac disease. There was 1 patient who experienced 10 TESAEs.

Table 56: Treatment-Emergent Serious Adverse Events: Safety Population

System Organ Class Preferred Term	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Total Number of TESAEs	29	11	40
Number of patients with at least 1 TESAE	16 (22.9)	9 (12.9)	25 (17.9)
Related	6 (8.6)	4 (5.7)	10 (7.1)
Unrelated	11 (15.7)	6 (8.6)	17 (12.1)
Blood and lymphatic system disorders			
Anaemia - Unrelated[1]	1 (1.4)	0	1 (0.7)
Febrile neutropenia - Related	0	1 (1.4)	1 (0.7)
Febrile neutropenia - Unrelated[2]	2 (2.9)	1 (1.4)	3 (2.1)
Leukopenia - Related	0	1 (1.4)	1 (0.7)
Neutropenia - Related[1]	1 (1.4)	0	1 (0.7)
Neutropenia - Unrelated[1]	1 (1.4)	0	1 (0.7)
Pancytopenia - Related[3]	1 (1.4)	0	1 (0.7)
Cardiac disorders			
Angina pectoris - Unrelated[4]	1 (1.4)	0	1 (0.7)
Atrial fibrillation - Unrelated[4]	1 (1.4)	0	1 (0.7)
Gastrointestinal disorders			
Constipation - Unrelated	1 (1.4)	0	1 (0.7)
Diarrhoea - Unrelated[2]	0	1 (1.4)	1 (0.7)
Ileus - Related	0	1 (1.4)	1 (0.7)
Small intestinal perforation - Unrelated[1]	1 (1.4)	0	1 (0.7)
General disorders and administration site conditions			
Pyrexia - Unrelated	0	1 (1.4)	1 (0.7)
Hepatobiliary disorders			
Cholecystitis - Unrelated	1 (1.4)	0	1 (0.7)
Immune system disorders			
Anaphylactic shock - Related[3]	1 (1.4)	0	1 (0.7)
Infections and infestations			
Abdominal infection - Unrelated[1]	1 (1.4)	0	1 (0.7)
Campylobacter gastroenteritis - Unrelated[1]	1 (1.4)	0	1 (0.7)
Encephalitis - Related[5]	0	1 (1.4)	1 (0.7)
Lower respiratory tract infection - Unrelated[6]	1 (1.4)	1 (1.4)	2 (1.4)
Pneumonia - Related	1 (1.4)	0	1 (0.7)
Pneumonia - Unrelated	2 (2.9)	0	2 (1.4)
Injury, poisoning and procedural complications			
Post procedural fistula - Unrelated[1]	1 (1.4)	0	1 (0.7)

Table 57: Treatment-Emergent Serious Adverse Events: Safety population (cont)

System Organ Class Preferred Term	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Subdural haematoma - Unrelated[5]	0	1 (1.4)	1 (0.7)
Investigations			
Liver function test abnormal - Related	1 (1.4)	0	1 (0.7)
Metabolism and nutrition disorders			
Hypoalbuminaemia - Unrelated[1]	1 (1.4)	0	1 (0.7)
Hypocalcaemia - Unrelated[1]	1 (1.4)	0	1 (0.7)
Hypomagnesaemia - Unrelated[1]	1 (1.4)	0	1 (0.7)
Tumour lysis syndrome - Related	1 (1.4)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease - Unrelated[6]	2 (2.9)	1 (1.4)	3 (2.1)
Pleural effusion - Unrelated	1 (1.4)	0	1 (0.7)
Pulmonary embolism - Unrelated[6]	1 (1.4)	0	1 (0.7)
Vascular disorders			
Deep vein thrombosis - Related	1 (1.4)	0	1 (0.7)
Thrombophlebitis - Unrelated	0	1 (1.4)	1 (0.7)

Abbreviation: TESAE, treatment-emergent serious adverse event.

Note: At each level of summarization, a patient was counted once if he or she reported 1 or more events. The event was considered to be related to study drug if the relationship was defined as 'possible', 'probable' or 'definite'.

1. Patient 3002-3002 experienced 10 TESAEs; Anaemia, Neutropenia (twice), Small intestinal perforation, Abdominal infection, Campylobacter gastroenteritis, Post procedural fistula, Hypoalbuminaemia, Hypocalcaemia, Hypomagnesaemia
2. Patient [redacted] experienced 2 TESAEs; Febrile neutropenia, Diarrhoea
3. Patient [redacted] experienced 2 TESAEs; Pancytopenia, Anaphylactic shock
4. Patient [redacted] experienced 2 TESAEs; Angina pectoris, Atrial fibrillation
5. Patient [redacted] experienced 2 TESAEs; Encephalitis, Subdural haematoma
6. Patient [redacted] experienced 3 TESAEs; Lower respiratory tract infection, Chronic obstructive pulmonary disease, Pulmonary embolism

Medical Dictionary for Regulatory Activities Version 18.1 was used. Combined preferred term was applied.

Deaths

There were no deaths reported during the Study CT-P10 1.1 and CT-P10 1.3. In the ongoing Phase 3 studies with CT-P10, 4 deaths were reported; 1 death in Study CT-P10 3.2 conducted with RA patients and 3 death in Study CT-P10 3.3 conducted with AFL patients.

By the data cut-off, a total of 3 deaths were reported in Cores Study Period CT-P10 3.3. Of these, 1 death due to an AE was reported after Core Cycle 1 and 2 deaths due to disease progression were reported during the Follow-up Period for patients who early discontinued the study treatment in the CT-P10 treatment group. The reported term of AE which led to death was tumour lysis syndrome (TLS) (1 [1.4%] patient in the CT-P10 treatment group). One death due to an AE was reported during the Core Study Period.

Laboratory findings

In Study CT-P10 1.1, the most common grade 3 finding was increased gammaglutamyltransferase (6 [5.9%] patients and 1 [2.0%] patients in CT-P10 group and Mabthera group, respectively). The most common grade 4 finding was decreased total neutrophils (2 [2.0%] patients and 3 [5.9%] patients in CT-P10 group and Mabthera group, respectively). Except 1 patient from each treatment group, these CTCAE grade 4 were not considered as TEAEs in the opinion of the investigators.

The most common grade 3/4 finding was decreased total neutrophils: 7 cases (7%) and 4 cases (8%), respectively. This was also the most common finding in Study CT-P10 1.3: 3 [8%] patients and 1 [5%] patients in the CT-P10 maintenance group and CT-P10 switch group, respectively; none was grade 4. In Study CT-P10 1.3, there were no notable differences between the CT-P10 maintenance and the CT-P10 switch groups in relation to clinical laboratory parameters.

For all other haematology, clinical chemistry, and urinalysis parameters, the mean changes from baseline in all studies were small, and there were no notable differences between the treatment groups. The majority of laboratory parameters had no CTCAE grade (i.e., the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE grade 1 (mild) or grade 2 (moderate) with transient changes over the time point in all clinical studies with CT-P10.

Study CT-P10 1.1

In Study CT-P10 1.1, post-baseline CTCAE grade 3 or higher for laboratory results are summarised. The most common grade 3 finding was increased GGT (6 [5.9%] patients and 1 [2.0%] patient in CT-P10 and Mabthera groups, respectively). The most common grade 4 finding was decreased total neutrophils (2 [2.0%] patients and 3 [5.9%] patients in CT-P10 and Mabthera groups, respectively) with similar proportions of patients higher grade 3 and 4; 7 (6.9%) patients and 4 (7.8%) patients in the CT-P10 and Mabthera group, respectively.

In Study CT-P10 1.1, 4 of 6 patients with CTCAE grade 3 or higher GGT level increase in the CT-P10 group had an ongoing medical history of GGT increase or pretreatment increased GGT level, or predisposing underlying diseases. Any predisposing factors and/or other underlying disease/conditions could not be identified for the other 2 patients in the CT-P10 group or a patient in the Mabthera group who have CTCAE grade 3 or higher GGT levels increase in the study. Excluding these patients with predisposing factors to the increased GGT levels, there was no difference observed between the CT-P10 and Mabthera groups. In addition, remaining 2 patients who had CTCAE grade 3 or higher result for GGT level increase in the CT-P10 group had received long-term NSAID treatment, which is considered as a predisposing factor to increased GGT.

Only small numbers of patients with severe GGT levels (Grade 3) are observed in Study CT-P10 1.1 with no cases of grade 4. In addition, there were no differences in the proportions of patients with severe (grade 3) or life-threatening (grade 4) GGT level increase observed in the larger study with RA patients, Study CT-P10 3.2. Furthermore, in the Study CT-P10 3.3 conducted in AFL patients, GGT level was not evaluated as GGT level was not an interested factor in CT-P10 AFL study, but no notable differences were observed in the proportion of patients reporting an event under Hepatobiliary disorder SOC (1 patient in each CT-P10 and Rituxan group) and clinical laboratory findings with LFT between the treatment groups.

A slightly higher rate of the increased GGT levels and decreased total neutrophil counts observed in the CT-P10 group in Study CT-P10 1.1 are not observed in the pooled safety data across the CT-P10 RA Studies (CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2) which shows no evidence of differences between the CT-P10 and the reference products. The laboratory results from Study CT-P10 1.1 on their own need to be viewed with caution due to the low number of events and the small number of patients assigned particularly to the Mabthera group as a result of the asymmetric randomisation allocation ratio (2:1).

Table 58: Summary of Patients with CTCAE Grade 3 or Higher Laboratory Results in Study CT-P10 1.1: Safety Population

Parameter CTCAE Grade	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)
	Number (%) of Patients	
Gamma-glutamyl transferase (GGT) increased		
Grade 3 (Severe)	6 (5.9)	1 (2.0)
Potassium, decreased		
Grade 3 (Severe)	0	2 (3.9)
Sodium, decreased		
Grade 3 (Severe)	1 (1.0)	0
Lymphocytes, decreased		
Grade 3 (Severe)	2 (2.0)	1 (2.0)
Total Neutrophils, decreased		
Grade 3 (Severe)	5 (4.9)	1 (2.0)
Grade 4 (Life-threatening)	2 (2.0)	3 (5.9)

Note: The summary was prepared based on the data of whole study period, including all post-baseline scheduled, unscheduled and repeat visits. Only the most severe result was counted when a patient reported the same event on more than one occasion.
CTCAE: Common Terminology Criteria for Adverse Events.

Study CT-P10 1.3 (Maintenance Study of CT-P10 1.1)

In Study CT-P10 1.3, there were no notable differences between the CT-P10 maintenance and the CT-P10 switch groups in relation to clinical laboratory parameters. The grade 3 finding reported in more than 1 patient in any treatment group were total neutrophils, decreased only (3 [7.9%] patients and 1 [5.0%] patient in CT-P10 maintenance group and CT-P10 switch group, respectively). Of these patients, only 1 patient in the CT-P10 switch group was reported as a TEAE. No post-baseline CTCAE grade 4 (life-threatening) laboratory results were reported.

Study CT-P10 3.2

In Study CT-P10 3.2, post-baseline CTCAE grade 3 or higher for laboratory results are summarised for the safety population. The most common grade 3 finding was GGT increased (2 [1.2%] patients in CT-P10 group, 3 [5.0%] patients in the Mabthera group and 4 [2.6%] patients in the Rituxan group). Grade 4 findings were reported for only 1 (0.6%) patient in the CT-P10 group, which was creatinine clearance (estimated by weight); in the CT-P10 group. This patient had ongoing medical history of hypothyroidism and reported a TEAE of acute renal failure which was considered by investigator to be unrelated to study drug.

Table 59: Summary of Patients with CTCAE Grade 3 or Higher Laboratory Results in Study CT-P10 3.2: Safety Population

Parameter CTCAE Grade	CT-P10 1000 mg (N=161)	MabThera® 1000 mg (N=60)	Rituxan® 1000 mg (N=151)	MabThera® + Rituxan® (N=211)
	Number (%) of Patients			
Hemoglobin, decreased				
Grade 3 (Severe)	1 (0.6)	0	3 (2.0)	3 (1.4)
Lymphocytes, decreased				
Grade 3 (Severe)	1 (0.6)	0	1 (0.7)	1 (0.5)
Total Neutrophils, decreased				
Grade 3 (Severe)	0	0	1 (0.7)	1 (0.5)
Creatine Phosphokinase (CPK), increased				
Grade 3 (Severe)	0	0	1 (0.7)	1 (0.5)
Creatinine, increased				
Grade 3 (Severe)	1 (0.6)[1]	0	0	0
Creatinine Clearance (Est by Weight), decreased				
Grade 4 (Life-threatening)	1 (0.6)[1]	0	0	0
Gamma-glutamyl Transferase (GGT), increased				
Grade 3 (Severe)	2 (1.2)	3 (5.0)	4 (2.6)	7 (3.3)
Glucose, decreased				
Grade 3 (Severe)	0	0	1 (0.7)	1 (0.5)
Sodium, decreased				
Grade 3 (Severe)	0	0	1 (0.7)	1 (0.5)

Note: Percentages were calculated using the number of subjects in the safety population as denominator. Only the most severe result was counted when a patient received the same tests in repeated visits.

[1] One patient ([redacted]) reported a TEAE of acute renal failure.

Study CT-P10 3.3

In Study CT-P10 3.3 (Part 1), post-baseline CTCAE grade 3 or higher for laboratory results are summarised for the safety population in table 63. The most common grade 3 or higher finding was neutrophil count decreased; 8 (13.6%) patients and 7 (11.3%) patients in CT-P10 and Rituxan groups, respectively.

Table 60: Summary of Patients with CTCAE Grade 3 or Higher Laboratory Results in Study CT-P10 3.3: Safety Population

Parameter CTCAE Grade	CT-P10 375 mg/m^2 (N=59)	Rituxan® 375 mg/m^2 (N=62)
	Number (%) of Patients	
Blood bilirubin, increased		
Grade 4 (Life-threatening)	2 (3.4)	2 (3.2)
Hyperuricemia		
Grade 4 (Life-threatening)	1 (1.7)	2 (3.2)
Hypoalbuminemia		
Grade 3 (Severe)	0	1 (1.6)
Hypocalcemia		
Grade 3 (Severe)	0	1 (1.6)
Hypokalemia		
Grade 4 (Life-threatening)	0	1 (1.6)
Neutrophil count decreased		
Grade 3 (Severe)	6 (10.2)	4 (6.5)
Grade 4 (Life-threatening)	2 (3.4)	3 (4.8)
White blood cell decreased		
Grade 3 (Severe)	3 (5.1)	3 (4.8)

Note: The Summary includes only the worst case during unscheduled and scheduled period. The Core Study Period includes the period from post drug administration of Cycle 1 to date of Cycle 5 infusion. In case of early discontinued subjects, Core Study Period includes the period from post drug administration to EOT1 visit.

CTCAE: Common terminology criteria for adverse events

There was a notable decrease in both neutrophil and whole blood cell (WBC) count from baseline in both treatment groups at each subsequent time point during the Core Study Period. There was no evidence of difference in mean change from baseline in all clinical chemistry and hematology laboratory parameters between the 2 treatment groups.

The majority of patients had normal baseline urinalysis results that remained normal during the Core Study Period in both treatment groups. The majority of clinical chemistry and hematology laboratory parameters was normal (as did not satisfy any CTCAE grade criteria) or was CTCAE grade 1 or grade 2 in intensity for each laboratory parameter and each subsequent time point.

Patients with CTCAE grade 3 or higher laboratory parameters during the Core Study Period are also summarized in table 64. The most commonly reported CTCAE grade 3 or higher laboratory parameter as worst value was neutrophil count decreased; grade 3 neutrophil count decreased was reported for 14 (20.0%) patients and 9 (12.9%) patients and grade 4 was reported for 5 (7.1%) patients and 5 (7.1%) patients in the CT-P10 treatment group and the Rituxan treatment group, respectively. The second most commonly reported CTCAE grade 3 laboratory parameter was white blood cell decreased (6 [8.6%] patients in each treatment group) and the following CTCAE grade 4 laboratory parameter was hyperuricemia (1 [1.4%] patient and 3 [4.3%] patients in the CT-P10 and Rituxan treatment groups, respectively).

Table 61: Summary of Patients With CTCAE Grade 3 or Higher during the Core Study Period: Safety Population

CTCAE Term	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
CTCAE Grade	Number (%) of Patients		
Clinical Chemistry			
Alanine aminotransferase increased			
Grade 3	3 (4.3)	0	3 (2.1)
Alkaline phosphatase increased			
Grade 3	1 (1.4)	0	1 (0.7)
Hypernatremia			
Grade 3	1 (1.4)	0	1 (0.7)
Hyperuricemia			
Grade 4	1 (1.4)	3 (4.3)	4 (2.9)
Hypoalbuminemia			
Grade 3	1 (1.4)	1 (1.4)	2 (1.4)
Hypocalcemia			
Grade 3	0	1 (1.4)	1 (0.7)
Grade 4	1 (1.4)	0	1 (0.7)
Hypokalemia			
Grade 3	0	1 (1.4)	1 (0.7)
Grade 4	1 (1.4)	1 (1.4)	2 (1.4)
Hyponatremia			
Grade 3	1 (1.4)	1 (1.4)	2 (1.4)
Hematology			
Neutrophil count decreased			
Grade 3	14 (20.0)	9 (12.9)	23 (16.4)
Grade 4	5 (7.1)	5 (7.1)	10 (7.1)
White blood cell decreased			
Grade 3	6 (8.6)	6 (8.6)	12 (8.6)

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.
Note: The summary included only the worst case during the unscheduled and scheduled visits. Core Study Period included from post drug administration of Cycle 1 to EOT1 visit.

Safety in special populations

Age

The use of CT-P10 has currently only been documented in studies involving subjects with rheumatoid arthritis, which is most prevalent in adults and the elderly. Twenty-five subjects over the age of 60 years have been treated in clinical studies with CT-P10. Dose adjustments on the grounds of advanced age are not required for rituximab. Age had no clinically significant effect on the pharmacokinetics of rituximab in patients treated for non-Hodgkin's lymphoma.

Summary of TEAEs in patients >65 years old included in the clinical trials

MedDRA Terms	Age <65 number (percentage)		Age 65-74 number (percentage)		Age 75-84 number (percentage)		Age 85+ number (percentage)	
	CT-P10 (N=284)	Rituxan + MabThera (N=277)	CT-P10 (N=45)	Rituxan + MabThera (N=49)	CT-P10 (N=3)	Rituxan + MabThera (N=6)	CT-P10 (N=1)	Rituxan + MabThera (N=0)
Total Number Of TEAEs	758	637	140	153	15	40	5	0
Number Of Patients With ≥ 1 TEAE	215 (75.7)	187 (67.5)	35 (77.8)	39 (79.6)	2 (66.7)	6 (100)	1 (100)	0
Total Number Of TESAEs	48	23	10	11	2	2	1 (100)	0
Number Of Patients With ≥ 1 TESAE	33 (11.6)	21 (7.6)	7(15.6)	9 (18.4)	2 (66.7)	2 (33.3)	1 (100)	0
- Fatal	1 (0.4)	0	1 (2.2)	0	0	0	0	0
- Hospitalization/prolong existing hospitalization	31 (10.9)	20 (7.2)	7 (15.6)	8 (16.3)	2 (66.7)	2 (33.3)	1 (100)	0
- Life-threatening	2 (0.7)	1 (0.4)	1 (2.2)	0	0	0	0	0
- Disability/incapacity	1 (0.4)	1 (0.4)	0	2 (4.1)	0	0	0	0
- Other (medically significant)	11 (3.9)	9 (3.2)	2 (4.4)	2 (4.1)	0	1 (16.7)	1 (100)	0
AE leading to drop-out	12 (4.2)	9 (3.2)	1 (2.2)	5 (10.2)	1 (33.3)	0	0	0
Psychiatric disorders	6 (2.1)	14 (5.1)	2 (4.4)	5 (10.2)	0	1 (16.7)	0	0
Nervous system disorders	33 (11.6)	39 (14.1)	10 (22.2)	9 (18.4)	1 (33.3)	1(16.7)	0	0
Accidents and injuries	0	0	0	0	0	0	0	0
Cardiac disorders	14 (4.9)	5 (1.8)	2 (4.4)	2 (4.1)	1 (33.3)	1 (16.7)	0	0
Vascular disorders	22 (7.7)	15 (5.4)	3 (6.7)	1 (2.0)	0	1 (16.7)	0	0
Cerebrovascular disorders	0	0	3 (6.7)	7 (14.3)	0	1 (16.7)	0	0
Infections and infestations	101 (35.6)	92 (33.2)	18 (40.0)	21 (42.9)	2 (66.7)	4 (66.7)	1 (100)	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased[1]	89 (38.2)	74 (32.5)	16 (55.2)	13 (38.2)	1 (100)	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia.	0	0	3 (6.7)	8 (16.3)	0	0	0	0

1 The results are from Studies CT-P10 1.1 and CT-P10 3.2 in RA patients. Patients whose (Baseline result – post-treatment result) equal to or higher than 0.8 for Physical Component Score (PCS) or Mental Component Score (MCS) were categorized into Quality of life decrease.

Patients with hepatic impairment

Rituximab is an immunoglobulin. It is not biotransformed in the liver, and does not undergo hepatic excretion. There is no evidence of hepatotoxicity in clinical use for the reference product (MabThera SmPC 2015; van Vollenhoven *et al.* 2010). No patients with clinically significant hepatic impairment have been treated in clinical trials with CT-P10.

Patients with renal impairment

Rituximab does not undergo renal excretion. There is no evidence of nephrotoxicity in clinical use for the reference product (MabThera SmPC 2015; van Vollenhoven *et al.* 2010). No patients with clinically significant renal impairment have been treated in clinical trials with CT-P10.

Sub-populations carrying known and relevant polymorphisms

FcγRIIIa receptor subtyping was performed on 96 subjects in the rheumatoid arthritis data set exposed to CT-P10 in Study CT-P10 1.1 and Study CT-P10 1.3. Approximately equal numbers of subjects with the FcγRIIIa FF variant (n=43) and the FcγRIIIa FF+VV variant (n=53) were treated with CT-P10.

Pregnancy and Lactation

Rituximab is not recommended to be administered during pregnancy. Women should be advised to avoid pregnancy during rituximab exposure and for 12 months after the last treatment has been administered.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed with CT-P10.

Discontinuation due to adverse events

In Study CT-P10 1.1, the proportion of patients who experienced at least 1 TEAE leading to permanent study drug discontinuation was similar between 2 treatment groups with 6 (5.9%) patients and 4 (7.8%) patients in the CT-P10 and Mabthera groups, respectively. The TEAE leading to permanent discontinuation from study treatments reported in more than 1 patient was infusion-related reaction (2 [2.0 %] patients in CT-P10 group). No other TEAE leading to permanent discontinuation from study treatments was reported for more than 1 patient in either treatment group.

In patients who received study drug in Maintenance Study Period (Study CT-P10 1.3), no TEAEs leading to permanent study drug discontinuation were reported.

Up to Week 24 in Study CT-P10 3.2, 3 (1.9%) patients in the CT-P10 group, 1 (1.7%) patient in the Mabthera group and 4 (2.6%) patients in Rituxan group experienced at least 1 TEAE leading to permanent discontinuation. The most frequently reported TEAE leading to permanent discontinuation was infusion related reaction in all of the 3 treatment groups (2 [1.2%] patients in the CT-P10 group, 1 [1.7%] patient in the Mabthera group and 3

[2.0%] patients in the Rituxan group). No other TEAEs leading to permanent discontinuation were reported for more than 1 patient in any of the 3 treatment groups.

In the pooled analysis, 9 patients each in the Total CT-P10 (CT-P10 + Switched to CT-P10) and the reference products (Mabthera + Rituxan) groups experienced at least 1 TEAE leading to permanent discontinuation. The most frequently reported TEAE leading to permanent discontinuation was infusion related reaction in both the Total CT-P10 and the reference products group, which were reported for 4 patients in each treatment group.

Up to Core Cycle 4 (12 weeks) in Study CT-P10 3.3, 3 (5.1%) patients in the CT-P10 group and 1 (1.6%) patient in the Rituxan group experienced at least 1 TEAE leading to permanent discontinuation. No TEAEs leading to permanent discontinuation were reported for more than 1 patient in the either treatment group. In Core Study Period treatment-emergent AEs leading to permanent study drug discontinuation were reported for 5 (7.1%) patients and 1 (1.4%) patient in the CT-P10 and Rituxan treatment groups, respectively. The TEAEs leading to permanent study drug discontinuation considered to be related to the study drug were reported for 3 (4.3%) patients and 1 (1.4%) patient in the CT-P10 and Rituxan treatment groups, respectively. Each TEAE was reported for only 1 patient. Regardless of the relationship with the study drug which was decided by the investigators, all patients had risk factors for the TEAEs leading to permanent study drug discontinuation, except one patient who early discontinued the study drug due to infusion-related reaction and the patient had positive results for ADA and NAb tests.

Table 62: Treatment-Emergent Adverse Events Leading to Permanent Study Drug Discontinuation by System Organ Class and Preferred Term: Safety Population

System Organ Class Preferred Term	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Number of patients with at least 1 TEAE leading to permanent study drug discontinuation	5 (7.1)	1 (1.4)	6 (4.3)
Cardiac disorders			
Angina pectoris - Unrelated	1 (1.4)	0	1 (0.7)
Infections and infestations			
Tuberculosis - Related	0	1 (1.4)	1 (0.7)
Injury, poisoning, and procedural complications			
Infusion related reaction - Related	1 (1.4)	0	1 (0.7)
Post procedural fistula - Unrelated	1 (1.4)	0	1 (0.7)
Investigations			
Liver function test abnormal - Related	1 (1.4)	0	1 (0.7)
Metabolism and nutrition disorders			
Tumour lysis syndrome - Related	1 (1.4)	0	1 (0.7)

Abbreviation: TEAE, treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities Version 18.1 was used. Combined preferred term was applied.

Overall, the proportions of patients who reported at least 1 TEAE leading to discontinuation were similar among the treatment groups across all CT-P10 studies and the indications. The comparative analysis did not reveal any trends or new signals in the patients treated with CT-P10.

Post marketing experience

No post-marketing data with CT-P10 are available.

2.5.1. Discussion on clinical safety

The clinical development programme comprises six studies, includes clinical studies in rheumatoid arthritis (RA) and non-Hodgking´s lymphoma (NLH) patients. Among the clinical studies of CT-P10, 2 Phase 1 studies in RA have been completed to date, Studies CT-P10 1.1 and CT-P10 1.3. And 3 Phase 3 studies are currently ongoing, which are Study CT-P10 3.2 in RA patients, Study CT-P10 3.3 in advanced follicular lymphoma (AFL) patients and Study CT-P10 3.4 in low tumour burden follicular lymphoma (LTBFL) patients.

Studies in rheumatoid arthritis (RA)

Treatment Emergent Adverse Events (TEAEs):

In Study CT-P10 1.1, TEAEs were reported for a total of 116 (75.8%) patients (71.6% in the CT-P10 group). The TEAEs most frequently reported in the CT-P10 group were upper respiratory tract infection (18.6%), infusion related reaction (11.8%), and urinary tract infection (10.8%). Overall, 46 (45.1%) patients in the CT-P10 group experienced TEAEs considered to be related to the study drug. The majority of TEAEs were grade 1 or grade 2 in intensity and no grade 4 TEAEs were reported. The proportion of patients who experienced at least 1 grade 3 TEAE was 13.7% in the CT-P10 group. The most frequently reported grade 3 TEAEs reported by patients was gamma-glutamyltransferase increased (2.0%) in the CT-P10 group. No other grade 3 or higher TEAEs were reported for more than 1 patient.

In Study CT-P10 1.3 (Maintenance Study of CT-P10 1.1), of those patients who received study drug in the Maintenance Study Period, 9/38 (23.7%) patients in the CT-P10 maintenance group and 4/20 (20.0%) patients in the CT-P10 switch group experienced at least 1 TEAE.TEAEs considered by the investigator to be related to study drug were reported for 2 (5.3%) patients and 2 (10.0%) patients in the CT-P10 maintenance group and CT-P10 switched group, respectively.The most frequently reported TEAEs in CT-P10 maintenance group were upper respiratory tract infection and urinary tract infection (each reported in 5.3%). In CT-P10 switch group, there was no TEAEs reported in more than 1 patient. All TEAEs considered by the investigator to be related to the study drug.The majority of TEAEs were grade 1 or grade 2 in intensity and no grade 4 TEAEs were reported. In Study CT-P10 1.3, 1 patient in the CT-P10 maintenance group experienced grade 3 hypertension and 1 patient in the CT-P10 switch group experienced grade 3 spinal osteoarthritis. Both TEAEs were considered unrelated to study treatment by investigator. No other grade 3 or higher TEAEs were reported.

In Study CT-P10 3.2, 95 (59.0%) patients in CT-P10 group, experienced at least 1 TEAE. Of these TEAEs, the most frequently reported was infusion related reaction in CT-P10 group (25 [15.5%] patients).

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), the proportions of patients reporting TEAEs were balanced between the treatment groups; 172 (60.8%) and 152 (58.0%) in the Total CT-P10 (CT-P10 only + Switched to CT-P10) and the reference products (Mabthera + Rituxan) groups, respectively. Of those, TEAEs considered by the investigator to be related to the study drug were reported for 97 (34.3%) patients and 90 (34.4%) patients in the Total CT-P10 (CT-P10 only + Switched to CT-P10) and the reference products groups, respectively. The majority of TEAEs were mild to moderate and their severities were similar between the 2 treatment groups. The TEAE most frequently reported was infusion related reaction in the Total CT-P10.

Treatment Emergent Serious Adverse Events (TESAEs):

In Study CT-P10 1.1, a total of 21 patients reported TESAEs; 14 (13.7%) patients experiencing 17 SAEs in the CT-P10 group and 7 (13.7%) patients experiencing 8 SAEs in the Mabthera group. The distribution of TESAEs is aligned with the randomization allocation of 2:1 in the study. The TESAEs that were considered by the

investigator to be related to study drug were reported for 3 (2.9%) patients and 2 (3.9%) patients in the CT-P10 and Mabthera group, respectively.

There was only 1 TESAE reported in more than 1 patient (intervertebral disc disorder, 2 [3.9%] patients in Mabthera group) and both cases were considered by the investigator to be unrelated to the study drug. No other TESAE was reported for more than 1 patient in either treatment group.

In Study CT-P10 1.3, among patients who received study drug in the Maintenance Study Period, 1 patient in each treatment group experienced a TESAE of spinal osteoarthritis. Both TEAEs were considered unrelated to study treatment by the investigator.No other TESAE were reported.

In Study CT-P10 3.2, a total of19 patients reported at least 1 TESAE; 10 (6.2%) patients in the CT-P10 group and 9 (6.0%) patients in the Rituxan group. No TESAE was reported in the Mabthera group. TESAEs considered to be related to the study drug were reported for 5 (3.3%) patients in the Rituxan group only. The most frequently reported TESAE in the CT-P10 group was fracture, which was reported for 2 (1.2%) patients, and no other TESAEs were reported for more than 1 patient in any of the 3 treatment groups.

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), TESAEs were reported for 26 (9.2%) patients and 16 (6.1%) patients in the Total CT-P10 and the reference products groups, respectively. The TESAE considered by the investigator to be related to the study drugs were reported for 3 (1.1%) patients and 7 (2.7%) patients in the Total CT-P10 and the reference products groups, respectively, and there were no related TESAEs that were reported for more than 1 patient in either treatment group.

Adverse Events of Special Interest (AESI):

Only few AESIs belonging to other risks groups were identified in the CT-P10 RA and AFL studies: IRRs, TLS, infections, opportunistic infections, malignancies, cardiovascular diseases and neutropenia. There were no reports of fatal infections, PML, SJS/TEN, HBV *de novo*, GI perforations, neurological disorders manifesting as PRES, AML / MDS.

Infusion Related Reactions (IRRs)

In Study CT-P10 1.1, 20 (19.6%) patients in the CT-P10 group experienced TEAEs of IRRs. Of these, there was no case with fatal outcome. The most frequently reported TEAEs of IRRs for patients in the CT-P10 group were infusion related reaction (11.8%), headache (4.9%) and dermatitis (2.0%).

In Study CT-P10 1.3, among the patients who received study drug in the Maintenance Study Period, 1 patient in each treatment group reported TEAEs of IRRs (2.6% and 5.0% in the CT-P10 maintenance and switch groups, respectively). No patients reported fatal, serious or severe IRR.

Overall, most IRRs were of mild to moderate severity and no fatal cases were reported throughout Studies CT-P10 1.1 and CT-P10 1.3. Severe (grade 3) events of IRRs were reported in 2 (2.0%) patients in the CT-P10 group only. IRR leading to the permanent study discontinuation were reported for 2 (2.0 %) patients in the CT-P10 group.

In Study CT-P10 3.2, the most frequently reported sign/ symptom of IRRs was pruritus and there were no notable differences in the reported symptom between the treatment groups.

Infections

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), 80 (28.3%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) reported at least 1 event of infection. The majority of events of infections were grade 1 (mild) and 2 (moderate) in severity whereas grade 3 (severe) events were

reported for 2 (0.7%) patients in the Total CT-P10. These events include an unrelated event of a urinary tract infection and an unrelated event of gastroenteritis in the Total CT-P10 group. Of those, none of events in the Total CT-P10 group were serious. There was 1 fatal event of infection in the Total CT-P10 group which was cellulitis. Serious events of infections were reported in 3 (1.1%) patients in the CT-P10.

Opportunistic Infections

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), 5 (1.8%) patients in the Total CT-P10 (CT-P10 + Switched to CT-P10) group reported at least 1 event of opportunistic infections. The majority of events of opportunistic infections were grade 1 (mild) and 2 (moderate) in severity No grade 3 (severe) or serious events were reported patients in the CT-P10 group.

Malignant Events

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), Grade 3 (severe) or serious events of malignancy were reported for 1 (0.4%) patient in the CT-P10. An additional malignant event reported for 1 patient in the Total CT-P10 group (Study CT-P10 3.2) was a grade 1 and non-serious event of thyroid neoplasm.

Impact on Cardiovascular Disease

In Study CT-P10 1.1, 14.7% patients in the CT-P10 group experienced TEAEs of cardiovascular nature. In Study CT-P10 1.3, 1 (2.6%) patient in the CT-P10 Maintenance group experienced a severe TEAE of hypertension which was ongoing from Study CT-P10 1.1.

When pooled across CT-P10 studies conducted in RA patients (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), the proportion of patients at least 1 event of cardiovascular disease were 25 (8.8%) patients in the Total CT-P10 group (CT-P10 + Switched to CTP10), and a higher proportion of patients have at least 1 risk factor for cardiovascular disease in the Total CT-P10 group; 158 (55.8%) patients in the Total CT-P10.

Neutropenia

In the pooled analysis for the RA population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), there was 5 (1.8%) patients in the Total CT-P10 group with neutropenia. In the NHL population (Study CT-P10 3.3), a slightly higher proportion of patients with neutropenia in the CT-P10 group was noted; 13 (22.0%).

Death:

There were no deaths reported during the Study CT-P10 1.1 and CT-P10 1.3. One death reported in Study CT-P10 3.2.

Laboratory findings

In Study CT-P10 1.1, the most common grade 3 finding was increased GGT (6 [5.9%] patients in CT-P10). The most common grade 4 finding was decreased total neutrophils (2 [2.0%] patients in CT-P10) with higher grade 3 and 4; 7 (6.9%) patients in the CT-P10.

In Study CT-P10 1.3, there were no notable differences between the CT-P10 maintenance and the CT-P10 switch groups in relation to clinical laboratory parameters (3 [7.9%] patients and 1 [5.0%] patient in CT-P10 maintenance group and CT-P10 switch group, respectively).

In Study CT-P10 3.2, the most common grade 3 finding was GGT increased (2 [1.2%] patients in CT-P10). Grade 4 findings were reported for only 1 (0.6%) patient in the CT-P10 group.

No differences in laboratory results were seen when taking into consideration results across all CT-P10 studies.

Discontinuation due to Treatment Emergent Adverse Events (TEAEs):

In Study CT-P10 1.1, the proportion of patients who experienced at least 1 TEAE leading to permanent study drug discontinuation was 5.9% in the CT-P10 group. The TEAE leading to permanent discontinuation from study treatments reported in more than 1 patient was infusion-related reaction (2.0 % in CT-P10 group).

In patients who received study drug in Maintenance Study Period (Study CT-P10 1.3), no TEAEs leading to permanent study drug discontinuation were reported.

Up to Week 24 in Study CT-P10 3.2, 3 (1.9%) patients in the CT-P10 group experienced at least 1 TEAE leading to permanent discontinuation. The most frequently reported TEAE leading to permanent discontinuation was infusion related reaction, 2 [1.2%] patients in the CT-P10 group.

In study CT-P10 3.2, the immunogenicity rate at week 24, which is the only time point with available information, did not appear comparable for the two products. In the randomised part 1 of the study, the ADA incidence in the CT-P10 arm (13.6%) was less than half that observed in the MabThera arm (27.6%).

Study in patients with Advanced Follicular Lymphoma (AFL)

Core Study Period CT-P10 3.3.

During the Core Study Period, patients were treated with study drug (CT-P10 or Rituxan) in combination with CVP for up to 8 cycles. Patients receiving at least 1 dose of CT-P10 were analyzed under the CT-P10 treatment group. Overall, CT-P10 was well tolerated and the safety profile of CT-P10 was comparable to that of Rituxan during the Core Study Period.

TEAEs: Treatment-emergent AEs were reported for 58 (82.9%) patients and 56 (80.0%) patients in the CT-P10 and Rituxan treatment groups, respectively. The most frequently reported TEAEs in the CT-P10 treatment group were neutropenia (24 [34.3%] patients) followed by IRR (16 [22.9%] patients) and constipation (12 [17.1%] patients). The majority of TEAEs were the CTCAE grade 1 or grade 2 in intensity. One grade 5 TEAE of tumour lysis syndrome was reported in the CT-P10 treatment group.

Treatment-emergent AEs considered by the investigator to be related to the study drug were reported for 37 (52.9%) patients in the CT-P10 treatment group and 34 (48.6%) patients in the Rituxan treatment group. The most frequently reported TEAEs considered by the investigator to be related to the study drug were neutropenia and IRR (15 [21.4%] patients each) in the CT-P10 treatment group and IRR (17 [24.3%] patients) followed by neutropenia (5 [7.1%] patients) in the Rituxan treatment group. The number of patients who experienced at least 1 grade 4 TEAE considered to be related to the study drug was 4 (5.7%) patients in each treatment group. The reported grade 4 TEAEs considered to be related to the study drug was neutropenia (4 [5.7%] patients in the CT-P10 treatment group and 3 [4.3%] patients in the Rituxan treatment group) and ileus (1 [1.4%] patient in the Rituxan treatment group).

TESAEs: Treatment-emergent SAEs during the Core Study Period were reported for 16 (22.9%) patients and 9 (12.9%) patients in the CT-P10 and Rituxan treatment groups, respectively. The proportion of patients who experienced at least 1 TESAE considered by the investigator to be related to the study treatment was similar in the 2 treatment groups (6 [8.6%] patients and 4 [5.7%] patients in the CT-P10 and Rituxan treatment groups, respectively).

AESI:

Treatment-emergent AEs due to IRRs during the Core Study Period were reported for 16 (22.9%) patients and 17 (24.3%) patients in the CT-P10 and Rituxan treatment groups, respectively.

Treatment-emergent AEs due to infection during the Core Study Period were reported for 22 (31.4%) patients and 26 (37.1%) patients in the CT-P10 and Rituxan treatment groups, respectively. The most frequently reported TEAEs due to infection in the CT-P10 treatment group were lower respiratory tract infection, pneumonia and upper respiratory tract infection (5 [7.1%] patients each). The most frequently reported TEAEs due to infection in the Rituxan treatment group was upper respiratory tract infection (12 [17.1%] patients). The number of patients with at least 1 of the respiratory infections (influenza, upper respiratory trac infection, tracheobronchitis, lower respiratory infection or pneumonia) was similar between the 2 treatment groups (16 [22.6%] patients in each treatment group). Furthermore, patients who had pneumonia or lower respiratory tract infection had risk factors regardless of the relationship with the study drug and they recovered without sequalae.

One TEAE classified as malignancy (basal cell carcinoma) was reported for 1 (1.4%) patient in the Rituxan treatment group.

No TEAEs due to PML were reported in either the CT-P10 or the Rituxan treatment group.

Discontinuation due to TEAEs: Treatment-emergent AEs leading to permanent study drug discontinuation during the Core Study Period were reported for 5 (7.1%) patients and 1 (1.4%) patient in the CT-P10 and Rituxan treatment groups, respectively. Of these, the number of patients considered to be related to the study drug was reported for 3 (4.3%) patients and 1 (1.4%) patient in the CTP10 and Rituxan treatment groups, respectively. Regardless of the relationship with the study drug, all of the patients had risk factors for the TEAEs leading to permanent study drug discontinuation, except 1 patient who early discontinued due to IRR and had a positive result for ADA and NAb tests at Core Cycle 4.

The proportions of patients who reported at least 1 TEAE leading to discontinuation were similar among the treatment groups across all CT-P10 studies and the indications. The comparative analysis did not reveal any trends or new signals in the patients treated with CT-P10.

Laboratory findings: The majority of laboratory parameters was normal (as did not satisfy any CTCAE grade criteria) or was CTCAE grade 1 or grade 2 in intensity for each laboratory parameter and each subsequent time point. Neutrophil count decreased was the most common CTCAE grade 3 or higher results laboratory parameters during the Core Study Period in the CT-P10 treatment group and the Rituxan treatment group (Grade 3: 14 [20.0%] patients and 9 [12.9%] patients; Grade 4: 5 [7.1%] patients and 5 [7.1%] patients, respectively).

The majority of patients had negative results for ADA and NAb tests during the Core Study Period. The proportion of patients with positive ADA results was similar in the 2 treatment groups during the Core Study Period (3 patients and 2 patients in the CT-P10 and Rituxan treatment groups, respectively). Mean IgM, IgG, and IgA levels were decreased from baseline through Cycle 8 of the Core Study Period, and there were no notable differences between the 2 treatment groups. The majority of patients had a grade 0 or grade 1 ECOG performance status at screening and at each subsequent visit. For other safety assessments, including vital signs, ECG, hypersensitivity monitoring, TB assessment, pregnancy test, and physical examination, there were no notable differences between the 2 treatment groups during the Core Study Period.

Deaths: During the Core Study Period, 1 death due to an AE was reported for a patient in the CT-P10 treatment group who died of tumour lysis syndrome (TLS). During the Follow-up Period, there were 2 more deaths caused by disease progression.

The most frequently reported TEAEs in the CT-P10 treatment group in Core Study Period (AFL patients) were neutropenia (24 [34.3%] patients).

In AFL patients, when compared Part 1 and Part 2 of Study CT-P10 3.3, the safety profile appears shlightly worse in Core Study Period (24 weeks) than in Part 1 (12 weeks).

From the safety database of rituximab all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics which follows the one of Mabthera.

2.5.2. Conclusions on the clinical safety

The overall safety profile of CT-P10 appeared roughly similar to that of the reference product although the pooled incidences of AEs and SAEs were generally lower for the reference products. Therefore, the available safety data are considered supportive of biosimilarity between CT-P10 and MabThera. Most common reported events were infections, infusion related reactions. The frequencies and nature of the adverse events were in line with those reported for the innovator MabThera/Rituxan in the RA and NLH study populations.

Although dataset of AFL patients has been updated, data are still considered very limited to reach firm conclusion about safety proflie. Additional safety data from maintenance study period CT-P10 3.3 and follow-up period should be provided (see RMP). The planned extension studies CT-P10 3.2 (RA) CT-P10 3.3 (AFL) and CT-P10 3.4 (LTBFL) listed in the RMP will provide additional long term safety data.

2.6. Risk Management Plan

The risk management plan covers several products indicated in different indications. Only the safety concerns listed for NHL, CLL and GPA/MPA are applicable to Blitzima.

2.6.1. Safety concerns

Table 63. Summary of the safety concerns

Summary of safety concerns	
Important identified risks (indication)	Infusion-related reactions (all indications) Infections including serious infections (all indications) Impaired immunisation response (all indications) Progressive multifocal leukoencephalopathy (PML) (all indications) Neutropenia (incl. prolonged) (all indications) Hepatitis B virus (HBV) reactivation (all indications) Tumour lysis syndrome (NHL/CLL) Gastrointestinal perforation (NHL/CLL) Hypogammaglobulinaemia (RA and GPA/MPA) Stevens-Johnson syndrome/Toxic epidermal necrolysis (all indications)

Summary of safety concerns	
Important potential risks (indication)	Posterior reversible encephalopathy syndrome (PRES) (all indications) Malignancy (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Prolonged B-cell depletion (all indications) Increased grade 3 or 4 and serious blood and lymphatic system adverse events in patients >70 years (CLL) Acute myeloid leukaemia/myelodysplastic syndrome (NHL/CLL) Second primary malignancy (NHL/CLL) Off-label use in autoimmune disease (RA and GPA/MPA) Off-label use in pediatric pateints (all indications) Relapse of GPA/MPA (GPA/MPA) Administration route error (NHL/CLL)
Missing information (indication)	Use during pregnancy or lactation (all indications) Immunogenicity and autoimmune disease (RA and GPA/MPA) Long-term use in GPA/MPA patients (GPA/MPA)

2.6.2. Pharmacovigilance Plan

Table 64: Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Phase III CT-P10 3.2 A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety between CT-P10, Rituxan® and MabThera® in Patients with Rheumatoid Arthritis Cat. 3	**Primary objective** Part 1 To evaluate and compare pharmacokinetics in terms of area under the serum concentration-time curve from zero to time of last quantifiable concentration (AUC_{0-last}), AUC from zero to infinity ($AUC_{0-\infty}$) and maximum serum concentration (C_{max}) of CT-P10 to Rituxan®, CT-P10 to MabThera® and Rituxan® to MabThera® during the first course of treatment (over the first 24 weeks). Part 2 To demonstrate that CT-P10 is similar to reference products (Rituxan® and MabThera®) in terms of efficacy as determined by clinical response according	Infusion-related reactions, infections including serious infections, impaired immunisation response, hypogamma-globuli naemia, PML, neutropenia, Hepatitis B virus (HBV) reactivation, SJS/TEN, malignancy, cardiovascular disease, prolonged B-cell depletion, use during pregnancy, immunogenicity and autoimmune disease	Started	CSR completed (up to 24 weeks): 3Q/2016 Estimated CSR completion (up to 76 weeks): 4Q/2017

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	to change from Baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP]) at Week 24. **Secondary objectives:** Part 1 To assess the additional PK variables of CT-P10, Rituxan® and MabThera®, during the first course of treatment (over the first 24 weeks). To evaluate the pharmacodynamics (PD) and safety of CT-P10, Rituxan® and MabThera® (over the first 24 weeks). Part 2 To evaluate the additional PK (up to Week 48), efficacy, PD, overall safety, and biomarkers of CT-P10 compared with reference products			
Phase III CT-P10 3.3 A Phase 1/3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison with Rituxan®, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma	**Primary objective:** Part 1 To demonstrate that CT-P10 is similar to US-licensed Rituxan® in terms of PK as determined by AUC_{tau} and C_{maxSS} at Cycle 4(Core Study period). Part 2 To demonstrate that CT-P10 is noninferior to Rituxan® in terms of efficacy as determined by overall response rate (CR + CRu + PR) over Cycle 8 (Core Study Period) according to the 1999 International Working Group (IWG) criteria **Secondary objective:** Part 1 To evaluate other PK	Infusion-related reactions, infections including serious infections, PML, neutropenia, Hepatitis B virus (HBV) reactivation, TLS, gastrointestinal perforation, PRES, SJS/TEN, secondary malignancy, AML/MDS, prolonged B-cell depletion, use during pregnancy, impaired immunisation response	Started	CSR completed (up to cycle 4): 2Q/2016 CSR completed (up to cycle 8): 4Q/2016 Estimated CSR completion (up to 3 years): 4Q/2019

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Cat. 3	parameters and pharmacodynamics (B-cell kinetics), overall safety, efficacy, and biomarkers of CT-P10 in comparison with Rituxan® Part 2 To demonstrate overall response rate (CR + PR) over 8 cycles (Core Study Period) according to the 2007 IWG criteria, and to evaluate additional efficacy parameters To evaluate pharmacodynamics (B-lymphocyte [B-cell] kinetics, including depletion and recovery), overall safety, and biomarkers of CT-P10 in comparison with Rituxan®.			

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Phase III CT-P10 3.4 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 Cat. 3	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, and biomarkers of CT-P10 in comparison with Rituxan®.	Infusion-related reactions, infections including serious infections, PML, neutropenia, Hepatitis B virus (HBV) reactivation, TLS, gastrointestinal perforation, PRES, SJS/TEN, secondary malignancy, AML/MDS, prolonged B-cell depletion, use during pregnancy, impaired immunisation response	Started	Estimated CSR completion (up to 7 months): 1Q/2020 Estimated CSR completion (up to 27 months): 4Q/2021

2.6.3. Risk minimisation measures

Table 65: Summary table of risk minimisation measures

Safety concern (indication)	Routine risk minimisation measures	Additional risk minimisation measures
Identified risk - Infusion-related reactions (all indications)	SmPC sections 4.2, 4.3, 4.4 and 4.8	RA/GPA/MPA patients only: • Physician information document
Identified risk - Infections including serious infections (all indications)	SmPC sections 4.2, 4.3, 4.4 and 4.8	RA/GPA/MPA patients only: • Physician information document • Patient information document • Patient Alert card
Identified risk - Impaired immunisation response (all indications)	SmPC section 4.4	None
Identified risk - Progressive multifocal leukoencephalopathy (PML) (all indications)	SmPC section 4.4 and 4.8	RA/GPA/MPA patients only: • Physician information document • Patient information document • Patient Alert card
Identified risk - Neutropenia (incl. prolonged) (all indications)	SmPC sections 4.3, 4.4 and 4.8	None
Identified risk - Hepatitis B virus (HBV) reactivation (all indications)	SmPC sections 4.3, 4.4 and 4.8	None
Identified risk - Tumour lysis Syndrome (NHL/CLL)	SmPC sections 4.2, 4.4 and 4.8	None
Identified risk - Gastrointestinal perforation (NHL/CLL)	SmPC section 4.8	None
Identified risk – Hypogammaglobulin-aemia (RA and GPA/MPA)	SmPC sections 4.3, 4.4 and 4.8	None
Identified risk - Stevens-Johnson syndrome/Toxic epidermal necrolysis (all indications)	SmPC sections 4.4 and 4.8	None
Potential risk - Posterior reversible encephalopathy syndrome (PRES) (all indications)	SmPC section 4.8	None
Potential risk - Malignancy (RA and GPA/MPA)	SmPC sections 4.4 and 4.8	None
Potential risk - Impact on cardiovascular disease (RA and GPA/MPA)	SmPC sections 4.3, 4.4 and 4.8	None

Safety concern (indication)	Routine risk minimisation measures	Additional risk minimisation measures
Potential risk - Prolonged B-cell depletion (all indications)	SmPC sections 4.8 and 5.1	None
Potential risk - Increased grade 3 or 4 and serious blood and lymphatic system adverse events in patients >70 years (CLL)	SmPC section 4.8	None
Potential risk - Acute myeloid leukaemia/myelodysplastic syndrome (NHL/CLL)	None	None
Potential risk - Second primary malignancy (NHL/CLL)	None	None
Potential risk - Off-label use in autoimmune disease (RA and GPA/MPA)	None	None
Potential risk - Off-label use in pediatric pateints (all indications)	SmPC section 4.2	None
Potential risk - Relapse of GPA/MPA (GPA/MPA)	SmPC section 5.1	None
Potential risk – Administration route error (NHL/CLL)	SmPC section 4.2	NHL/CLL patients only: • Physician information
Missing information - Use during pregnancy or lactation (all indications)	SmPC section 4.6	None
Missing information - Immunogenicity and autoimmune disease (RA and GPA/MPA)	SmPC section 5.1	None
Missing information - Long-term use in GPA/MPA patients (GPA/MPA)	SmPC section 5.1	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The applicant has submitted a document for justify that Blitzima is a duplicate licence application of Truxima. The bridging report between Truxima and MabThera has already been accepted by the EMA during the review of centralised procedure for original MAA of Truxima. There are no significant changes in content and design for the proposed patient leaflet (PL) and Truxima PL, except for proprietary name and a few indication-specific sections. Therefore, the company´s justification to not undertake further consultation with target patient groups, is considered acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Blitzima (rituximab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The therapeutic context of rituximab is very well described over the years since it first received the MA in the EU (2nd June 1998), as Mabthera.

Truxima (rituximab), being a biosimilar of MabThera is reviewed in the context of its similarity and comparability with the reference product.

3.2. Favourable effects

PK analyses for study CT-P10 1.1 demonstrate that the PK profiles of CT-P10 and MabThera are comparable. In addition to the analyses of PK from Study CT-P10 1.1, which compared CT-P10 and Mabthera, Study CT-P10 3.2, which compared CT-P10, Mabthera and Rituxan, and Study CT-P10 3.3, which compared CT-P10 and Rituxan, support the conclusion of PK similarity. In addition, PK data in both RA and AFL patients support the extrapolation to all other indications.

In study CT-P10 1.1. mean B-cell levels BLOQ (20 cells/µl) were reached at the end of infusion in the CT-P10 arm. All patients but one in the Mabthera arm had reached levels below 20 cells/µl within 15 minutes after infusion end. In both study arms B-cell counts consistently remained below 20 cells/µl until week 16 for the majority of patients. In study CT-P10 3.2. the B-cell counts from all patients, except one in the CT-P10 group, decreased to below the LLoQ (20 cells/µL) immediately after the 1st infusion and then remained below this level up to Week 24 in the majority of patients in all treatment groups.

In study CT-P10 3.3. in AFL patients, a sharp decrease was observed in mean B-cell counts 1 hour after the end of infusion at Core Cycle 1 and a complete depletion (below LLoQ) was achieved at Cycle 4 for both CT-P10 and Rituxan treatment groups.

On the basis of the clinical data submitted from the Study CT-P10 1.1 and 3.2, both treatments seem similar in terms of ACR up to week 24. Regarding the change from baseline in the disease activity measured by DAS28 in Study CT-P10 1.1 and 3.2, the analyses carried out by the applicant meet the criteria for therapeutic equivalence according to the equivalence margin of 0.60.

In the study 3.3, in terms of the ORR 1999 IWG criteria (central review) both in PP and ITT population, the difference lies within 7% (4.3% and 5.7% PP and ITT respectively), therefore comparability to the reference rituximab is demonstrated.

3.3. Uncertainties and limitations about favourable effects

In the Oncology setting, analyses on ORR as per the 2007 IWG criteria, time-to-event parameters including PFS, TTP, TTF, response duration, DFS and OS will be submitted when available and in the case of PFS and OS, yearly updates will be required (see RMP) as patients who experienced CR, CRu, or PR after Cycle 8 of the Core Study Period will enter in the Maintenance Study Period with Rituximab monotherapy.

3.4. Unfavourable effects

The type and incidence of ADRs to CT-P10 and the reference product were broadly comparable and for most in line with those expected on the basis of the MabThera SmPC.

3.5. Uncertainties and limitations about unfavourable effects

There are inherent limitations due to the size of the biosimilar product safety database for the purpose of characterization and evaluation of rare events of special interest.

The clinical relevance of Human anti-chimeric antibodies (HACA) formation in rituximab-treated patients remains not fully understood. In general, the proportion of patients with positive ADA titres was similar in the CT-P10 and MabThera treatment groups during the study. The majority of patients had negative ADA test results at each time point in Studies CT-P10 1.1 and CT-P10 1.3. However, in study 3.2 (part 1) the HACA incidence at week 24 (only time point available) in the CT-P10 arm (13.6%) was less than half that observed in the MabThera arm (27.6%).

Otherwise, the safety profile of the two products appears broadly comparable except for a higher number of infusion related reaction, nausea, vomiting, general disorders and administration site conditions (pyrexia), neutropenia, upper respiratory tract infection, urinary tract infection dizziness and rheumatoid arthritis in the CT-P10 arms. These numbers are too small to conclude at this stage; longer term data and a larger database in the post-marketing setting are required. Additional safety data from Maintenance Study Period CT-P10 3.3. (up to 2 years) and Follow-up Period (until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient) will be provided (see RMP).

3.6. Effects Table

N/A

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A comprehensive biosimilarity exercise, which covered all relevant structural and functional characteristics of the rituximab molecule, was submitted. The presented results support the biosimilarity claim; similarity between CT-P10 and the EU reference product MabThera is considered demonstrated at the quality level. Any minor differences observed have been adequately justified with respect to the efficacy/safety profile of Truxima.

Based on the data submitted, in terms of ACR criteria and importantly in terms of DAS28 it could be reasonable to assume the similarity of both products. The similarity based on the margin of ± 0.6 for analysis of therapeutic equivalence in CT-P10 1.1 and 3.2 studies was met. In addition, both products seem to obtain similar results in the individual components of ACR criteria.

Both the PK package and the pivotal efficacy trial in patients with rheumatoid arthritis (ACR20 at week 24) achieved their respective primary and important secondary endpoints (e.g. DAS28 and ACR 20 across whole study period) which is considered crucial for the biosimilar exercise and support the extrapolation to all other indications. From a clinical point view, rheumatology studies point out a clear similarity based on DAS28 and ACR criteria.

From an oncology perspective, and bearing in mind the extrapolation to oncology indications, the objectives of study CT-P10 3.3 were to demonstrate similarity in pharmacokinetics and non-inferiority in efficacy of CT-P10 to Rituxan as primary endpoints when coadministered with CVP in patients with advanced FL. Overall and in the framework of supportive data from study CT-P10 3.3, these objectives have been met. The oncology study in AFL highlight the similarity based on ORR after 8 cycles of treatment. The latter would support the extrapolation to oncology indications. The results from all other efficacy endpoint in Study CT-P10 3.3 will be available with the final CSR by 4Q/2019.

Additionally, the safety profile of Truxima seems similar compared to Mabthera with any observed differences in antibody formation not having any clinical meaningful impact on the efficacy. Updates on safety will be submitted with the final CSRs of the ongoing studies (see RMP).

3.7.2. Balance of benefits and risks

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.

The acceptance of a biosimilar product is based on the overall similarity of quality, pharmaco-toxicological, pharmacokinetic and pharmacodynamic aspects and clinical efficacy and safety. This includes comprehensive physicochemical, biological characterisation and comparison and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product. Any observed differences have to be justified also with regard to their potential effect on efficacy and safety of the biosimilar medicinal product.

Biosimilarity at quality level was demonstrated on the basis of a very comprehensive comparability exercise. From a non-clinical perspective comparative PD, PK and toxicokinetic data between Truxima and the reference product Mabthera demonstrated biosimilarity.

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

The efficacy of Truxima was shown to be similar to that of Mabthera in the primary endpoint (ACR20, week 24) and the other secondary endpoints. Therefore these results are sufficient to demonstrate equivalence in efficacy between the proposed biosimilar Truxima and the reference product Mabthera.

Extrapolation of these conclusions other authorised indications for rituximab is sufficiently justified.

Finally, with regards to safety, the adverse event profiles, clinical laboratory data, and other safety parameters did not show any significant safety issues which are not expected with rituximab treatment. There were no obvious relevant differences in the safety profile of Truxima as compared to Mabthera with no obvious no indication of any safety imbalance in disadvantage of Truxima. The safety outcomes obtained with Truxima in RA and AFL patients can be reasonably extrapolated to the other approved therapeutic indications of EU Mabthera. There appears to be no relevant differences in the safety profile of rituximab throughout the approved therapeutic indications. As a biosimilar, the safety-related product information for Mabthera also applies to Truixima.

In conclusion, the safety profile of Truxima seems highly comparable to Mabthera with the inherent limitations due to the lack of data in the long run, which is not considered worrisome in itself. Additional long term safety data will be provided from the extension studies through RMP measures.

3.7.3. Additional considerations on the benefit-risk balance

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.

The applicant intends to claim the same therapeutic indications for adult patients for the biosimilar Truxima as granted for Mabthera for iv administration in the EU. However, as Mabthera is also marketed in the subcutaneous indication, a risk of medication error has been identified. Adequate risk minimisation measures to avoid the potential route of administration error have been included in the RMP.

3.8. Conclusions

The application for Blitzima was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a duplicate of Truxima authorised on 17 February 2017.

The overall Benefit Risk balance is considered positive in the following claim indications:

Non-Hodgkin's lymphoma (NHL)

Blitzima is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Blitzima maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Blitzima monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.

Blitzima is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Blitzima in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Blitzima or patients refractory to previous Blitzima plus chemotherapy.

Granulomatosis with polyangiitis and microscopic polyangiitis

Blitzima, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Blitzima is not similar to Imbruvica (Ibrutinib), Arzerra (Ofatuzumab), Gazyvaro (Obinutuzumab) and Venclyxto (Venetoclax) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Blitzima is favourable in the following indication:

Non-Hodgkin's lymphoma (NHL)

Blitzima is indicated for the treatment of previously untreated patients with stage III IV follicular lymphoma in combination with chemotherapy.

Blitzima maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Blitzima monotherapy is indicated for treatment of patients with stage III IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.

Blitzima is indicated for the treatment of patients with CD20 positive diffuse large B cell non Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Blitzima in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Blitzima or patients refractory to previous Blitzima plus

chemotherapy.

See section 5.1 for further information.

Granulomatosis with polyangiitis and microscopic polyangiitis

Blitzima, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Non-Oncology indications:

The MAH must ensure that all physicians who are expected to prescribe Blitzima are provided with the following:

- Product information
- Physician information
- Patient information
- Patient Alert card

The Physician information about Blitzima should contain the following key elements:

- The need for close supervision during administration in an environment where full resuscitation facilities are immediately available
- The need to check, prior to Blitzima treatment, for infections, for immunosuppression, for prior/current medication affecting the immune system and recent history of, or planned, vaccination

- The need to monitor patients for infections, especially PML, during and after Blitzima treatment
- Detailed information on the risk of PML, the need for timely diagnosis of PML and appropriate measures to diagnose PML
- The need to advise patients on the risk of infections and PML, including the symptoms to be aware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The Patient information about Blitzima should contain the following key elements:

- Detailed information on the risk of infections and PML
- Information on the signs and symptoms of infections, especially PML, and the need to contact their doctor immediately if they experience any
- The importance of sharing this information with their partner or caregiver
- Information on the Patient Alert Card

The Patient Alert Card for Blitzima in non-oncology indications should contain the following key elements:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur

Oncology indications:

The MAH must ensure that all physicians who are expected to prescribe Blitzima are provided with the following:

- Product information
- Physician information

The Physician information about Blitzima should contain the following key elements:

- Information that the product should be administered as IV only to avoid administration route errors.

The Physician information and Patient information must be agreed with the National Competent Authorities prior to distribution and Patient Alert Card should be included as part of inner packaging.