Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Names: Truxima, Ritemvia

Sponsor: Celltrion Healthcare Australia Pty. Ltd.

August 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody dependent cellular cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
AE	Adverse event
AFL	Advanced follicular lymphoma
ANCA	Anti-neutrophil cytoplasmic antibody
ANOVA	Analysis of variance
ASTM	Autologous stem cell transplant
AUC_{inf}	Area under concentration-time curve from time zero to infinity
AUC_{tau}	Area under concentration-time curve from time zero to steady state
$AUC_{0\text{-last}}$	AUC-time curve from time zero to last detectable drug concentration
BLOQ	Below limit of quantification
BMI	Body mass index
BSA	Body surface area
CCP	Cyclic citrullinated peptide
CD	Cluster of differentiation
CDAI	Clinical disease activity index
CDC	Complement dependent cytotoxicity
CHMP	Committee on Medicinal Products for Human Use (EMA)
CL	apparent drug clearance
CLL	Chronic lymphocytic leukaemia
CI	Confidence interval
C_{max}	Maximum serum concentration

Abbreviation	Meaning
C_{min}	Minimum serum concentration
C_{trough}	Trough serum concentration
CR	Complete response
CRu	unconfirmed complete response
CRP	C-reactive protein
CS	Corticosteroids
CSF	Colony stimulating factor
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CVP	Cyclophosphamide, vincristine and prednisone
DAS	Disease activity score
DLBCL	Diffuse large B-cell lymphoma
DMARD	Disease modifying anti-rheumatic drug
ECL	Electro chemiluminescent
ECOG	Eastern Cooperative Oncology Group
EPAR	European public assessment report
EOT	End of treatment
ES	Erosion score
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FcγR	Fc gamma receptor
FcRn	Neonatal Receptor for IgG
FLIPI	Follicular lymphoma international prognostic index
GCP	Good clinical practice
GPA	Granulomatosis with polyangiitis

Abbreviation	Meaning
HACA	Human anti-chimeric antibody (also ADA anti-drug antibody)
HAQ	Health assessment questionnaire
Ig	Immunoglobulin
IRR	Infusion related reaction
ITT	Intention to treat
IV	Intravenous
IWG	International Working Group
JSN	Joint space narrowing
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LS	Least squares
MPA	Microscopic polyangiitis
mTSS	Modified total Sharp score
MTX	Methotrexate
NAb	Neutralising antibodies
NHL	Non-Hodgkin's lymphoma
NSAID	Non-steroidal anti-inflammatory drug
OS	Overall survival
ORR	Overall response rate
PAC	Patient alert card
PD	Pharmacodynamic
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Per protocol
PR	Partial response

Abbreviation	Meaning
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RTX	Rituximab
SAE	Serious adverse event
SD	Standard deviation
SDAI	Simplified disease activity index
SE	Standard error
SOC	System organ class
TB	Tuberculosis
T_{max}	Time to C_{max}
TNF	Tumour necrosis factor
$T_{1/2}$	Terminal elimination half-life
ULN	Upper limit of normal
VAS	Visual analog scale (pain in arthritis)
Vd	apparent volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar
Decision:	Approved
Date of decision:	16 February 2017
Date of entry onto ARTG:	15 April 2018, 16 April 2018
ARTG numbers:	285815, 285816, 285817, and 285818
, *Black Triangle Scheme*	No
Active ingredient:	Rituximab
Product names:	Truxima; Ritemvia
Sponsor's name and address:	Celltrion Healthcare Australia Pty. Ltd.[1] Level 7/9 Castlereagh St., Sydney NSW
Dose form:	Concentrate for injection
Strengths:	500 mg in 50 mL; 100 mg 10 mL
Containers:	Type 1 glass vial 10 mL and 50 mL
Pack sizes:	1 x 500 mg/50 mL vial 2 x 100 mg/10 mL vial
Approved therapeutic use:	*Non-Hodgkin's Lymphoma (NHL)* *Truxima / Ritemvia (rituximab) is indicated for treatment of patients with:* • *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,* • *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,* • *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.* *Chronic Lymphocytic Leukaemia (CLL)* *Truxima / Ritemvia (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.*

[1] The sponsor during the application process was Pharmbio Pty Ltd and was subsequently changed after registration to the current sponsor Celltrion Healthcare Australia Pty Ltd

	Rheumatoid Arthritis (RA) *Truxima / Ritemvia (rituximab) 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 at least one tumour necrosis factor (TNF)inhibitor therapy.* *Truxima / Ritemvia (rituximab) has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.* *Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis(MPA)* *Truxima / Ritemvia (rituximab) in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with rituximab have not been established.*
Route of administration:	Intravenous infusion
Dosage:	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia: 375 mg/m^2 body surface area weekly for 4 weeks in combination with other chemotherapy and steroid or Rheumatoid arthritis: two 1000 mg infusions two weeks apart

Product background

This AusPAR describes the application by the sponsor to register a biosimilar monoclonal antibody Truxima/Ritemvia rituximab concentrate for injection for the following indications:

Non-Hodgkin's Lymphoma (NHL)

- *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.*

Chronic Lymphocytic Leukaemia (CLL)

Truxima is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis (RA)

Truxima (rituximab) 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 at least one tumour necrosis factor (TNF) inhibitor therapy.

Truxima has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with rituximab have not been established.

The requested indications are the same as currently approved for MabThera administered by intravenous infusion (see Section: *Regulatory status*, below). MabThera is also approved for subcutaneous use in the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia but the product has a different formulation from the intravenous solution. A subcutaneous formulation was not included in the submission. The sponsor proposed two trade names, Truxima, and Ritemvia.

Rituximab is a chimeric murine/human immunoglobulin (IgG1) monoclonal antibody containing murine light and heavy chain variable region sequences (Fab domain) and human constant region sequences (Fc domain) that bind with high affinity and specificity to the CD20 antigen found on the surface of normal and malignant B-cells in humans. The proposed therapeutic mechanism of action of rituximab is to promote B-cell lysis via complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis.

Regulatory status

Rituximab was first registered in Australia in October 1998 as MabThera as a concentrate for intravenous infusion. Subsequent approval of rituximab biosimilar products for intravenous use were Ristova (AUST R 291815, 291816); and in 2017, Riximyo (AUST R 271781, 281782), Rixonfya (AUST R 309669, 309670) and Rixvyda (AUST R 309667, 309668).

Table 1: International regulatory status

Country	Dosage Form(s)	Indication(s)	Status/ Date
Korea (as Truxima)	500 mg/vial concentrate for solution for infusion	Non-Hodgkin's lymphoma(NHL) Chronic lymphocytic leukaemia(CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Approved 16 November 2016
European Union (as Truxima)	500 mg/vial concentrate for solution for infusion	Non-Hodgkin's lymphoma(NHL) Chronic lymphocytic leukaemia(CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Submitted 12 October 2015
Malaysia (as Truxima)	500 mg/vial concentrate for solution for infusion	Non-Hodgkin's lymphoma(NHL) Chronic lymphocytic leukaemia (CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Submitted 1 December 2016

Country	Dosage Form(s)	Indication(s)	Status/ Date
Philippines (as Truxima)	500 mg/vial concentrate for solution for infusion	Non-Hodgkin's lymphoma (NHL) Chronic lymphocytic leukaemia (CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Submitted on 6 December 2016
Thailand (as Truxima)	500 mg/50 mL concentrate for solution for infusion	Non-Hodgkin's lymphoma (NHL) Chronic lymphocytic leukaemia (CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Submitted 15 December 2016
Turkey (as Truxima)	500 mg/50 mL concentrate for solution for infusion	Non-Hodgkin's lymphoma (NHL) Chronic lymphocytic leukaemia (CLL) in combination with chemotherapy Rheumatoid arthritis in combination with methotrexate Granulomatosis with polyangiitis and microscopic polyangiitis combination with glucocorticoids	Submitted 30 December 2016

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2017-00695-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2017
First round evaluation completed	1 September 2017
Sponsor provides responses on questions raised in first round evaluation	26 October 2017
Second round evaluation completed	1 December 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	21 December 2017

Description	Date
Sponsor's pre-Advisory Committee response	11 January 2018
Advisory Committee meeting	1 – 2 February 2018
Registration decision (Outcome)	13 March 2018
Completion of administrative activities and registration on ARTG	17 April 2018
Number of working days from submission dossier acceptance to registration decision*	199

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Truxima (company code: CT-P10) drug substance (rituximab) is a chimeric monoclonal IgG1 antibody with kappa light chains. 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.

Figure 1: A schematic structure of CT-P10 (Truxima, rituximab)

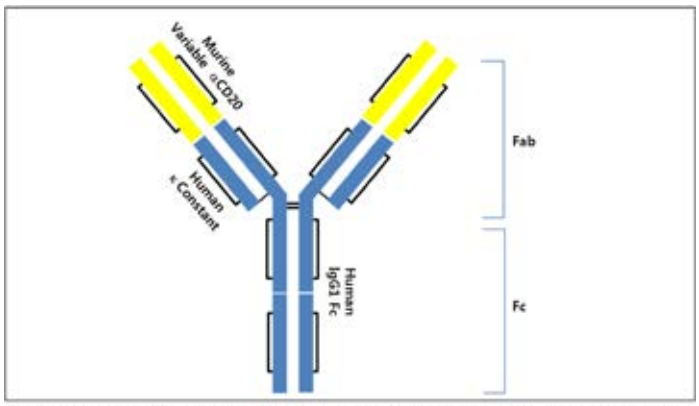


Figure 3.2.S.1.2-2: Schematic Diagram of CT-P10: Variable Region (Yellow) and Constant Region (Blue)

Drug substance (active ingredient)

The amino acid sequences of the heavy and light chains were based on those of the published amino acid sequence for rituximab. The hypervariable regions of the antibody impart specificity to human CD20. The primary amino acid sequence was confirmed by peptide mapping with mass spectrometry analysis.

Higher order structure analysis examining disulphide bond locations, Fourier transformation infrared spectroscopy, differential scanning calorimetry and circular dichroism indicated that the molecule showed features consistent with those of an IgG1 antibody.

Truxima 100 mg/10 mL, rituximab, has been developed as a similar biological medicinal product (biosimilar) to that of the currently registered reference product MabThera (AUST R 60319) 500 mg/50 ml and MabThera (AUST R 60318) 100 mg/10 mL.

During the development of Truxima/Ritemvia, EU-sourced MabThera and US-sourced Rituxan (licensed name in US) was used as the main reference product to demonstrate biosimilarity in terms of quality and non-clinical comparability exercise. An additional bridging comparability study was performed between EU-sourced and AU-sourced MabThera to present EU-sourced MabThera as representative of the Australian registered product (AUST R 60319 MabThera 500 mg/50 ml and AUST R 60318 MabThera 100 mg/10 mL).

Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that Truxima/Ritemvia and European sourced MabThera are generally similar. Subtle differences were seen between Truxima/Ritemvia and MabThera/Rituxan (EU and US sourced respectively). Thus batches of Truxima/Ritemvia, showed lower concentrations of high molecular weight proteins, slightly altered species of protein as detected by isoelectric focussing and slightly different distributions of glycan isoforms. These subtle differences appear to have no obvious impact on the function or stability of Truxima/ Ritemvia, with the sponsor providing adequate data to support this.

Overall, the sponsor has demonstrated that Truxima/Ritemvia is comparable to MabThera in terms of structure, species, function and degradation profile (that is, physicochemically and biologically).

There is no pharmacopoeial monograph for rituximab. The specifications for the drug substance were based on the European Pharmacopoeial general monograph requirements for recombinant substances to be used in injections and in comparison with the reference material MabThera.

Drug product

Specifications for the drug product were based on the European pharmacopoeial general monograph requirements for sterile products for injection.

The proposed shelf life for the 500 mg presentation is 36 months when stored at 5°C, while the proposed shelf life for the 100 mg presentation is 24 months when stored at 5°C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the diluted product are 24 hours when stored at 5°C with a subsequent 24 hours at 30°C.

No data has been presented in terms of excursions however the sponsor has indicated they intend to undertake such studies.

There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Truxima and Ritemvia have been controlled to an acceptable level.

Biopharmaceutics

Bioequivalence studies were not required.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Truxima/ Ritemvia. Minor deficiencies are noted in terms of manufacturing clearance approval.

Truxima /Ritemvia are rituximab biosimilars which were compared to Rituxan (US approved) and MabThera (European approved), including Australian sourced MabThera, and showed considerable similarity in biophysical and in vitro activity assays.

With respect to quality matters, the PI, Consumer Medicine Information (CMI) and labels are acceptable.

IV. Nonclinical findings

Introduction

The sponsor has applied to register Truxima, rituximab, as a biosimilar to MabThera. Truxima is proposed to be used for the same indications as MabThera (as described above).

The dosage and administration instructions for Truxima match those contained in the approved Australian PI for MabThera. The proposed dosing regimen involves intravenous infusion, with the dose and frequency of administration varying with the indication.

The scope of the submitted non-clinical section of the dossier was in general accordance with the relevant guideline;[2] containing comparative in vivo pharmacology (in the toxicity study), pharmacokinetic and toxicity studies. Comparative in vitro pharmacology studies were evaluated in this report.

The in vivo and ex vivo studies used early batches on Truxima. The in vitro pharmacology studies used clinical and commercial batches of Truxima. No comparative studies were submitted that assessed the function of the early and clinical/commercial batches of Truxima. This is not considered a major concern as no significant difference in function was evident between the early batches of Truxima and the reference product, and there was no significant difference in function between the clinical/commercial batches of Truxima and the reference products, even though different assays were performed.

The EU and US sourced MabThera and Rituxan, respectively, were used as comparators in the nonclinical studies. The Australian-sourced MabThera was not used, and no data were provided to verify the comparability of the various sources of MabThera. Provided adequate comparability of the EU/US sourced and Australian sourced versions of MabThera is demonstrated in the quality module, the submitted non-clinical dossier is considered adequate.

[2] EMA/CHMP/BMWP/ 403543/2010; Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues

Pharmacology

Rituximab is a monoclonal antibody directed against CD20, exerting its effects via antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC) and apoptosis.

The in vitro pharmacology studies assessed the essential functions of this activity (CD20 binding, Fc receptor binding, binding to the complement component, C1q, and ADCC, CDC and apoptotic activity). A sufficient number of batches (15) were examined. There was no significant difference between Truxima, EU sourced MabThera and US sourced Rituxan in terms of: CD20 affinity, apoptosis, ADCC and CDC of CD20 expressing cells, binding affinity to FcRn, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (F and V Type) and FcγRIIIb, and C1q binding affinity.

In monkeys receiving Truxima, B cell depletion (associated with the primary pharmacology of rituximab) was evident in the peripheral blood and lymphoid tissues (spleen, lymph node). The extent of B cell depletion was generally similar to that seen for EU MabThera.

The combined data suggest a similar pharmacological profile for Truxima and EU MabThera. No specific comment can be made from a nonclinical perspective regarding comparative efficacy in any of the proposed indications.

Pharmacokinetics

There were no obvious or meaningful differences in pharmacokinetic parameters between Truxima and EU MabThera in cynomolgus monkeys following IV dosing at equivalent doses. Bioequivalence in humans was claimed.

A tissue cross reactivity study with Truxima and EU MabThera against human tissues suggested a similar profile.

Toxicology

One comparative GLP-compliant repeat dose toxicity study of 6 to 7 weeks duration was submitted. The toxicity profile of Truxima in cynomolgus monkeys was compared with that of EU MabThera. The duration of the study and the choice of species are considered acceptable. The clinical route (IV) was used. The doses chosen and dosing regimen (once weekly) are acceptable, consistent with those used in the original submission for MabThera.

The most notable finding with Truxima in the toxicity study was B cell depletion (peripheral blood, lymphoid tissues) and decreased germinal centres in lymphoid tissues, consistent with the expected pharmacological action of rituximab. No unanticipated toxicities were observed with Truxima.

The nature, incidence and severity of findings with Truxima were generally comparable to those observed with EU sourced MabThera. Anti-drug antibody incidence and injection site reactions were similar in animals that received either one of the two test items.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[3] This matches the existing category for MabThera and is considered appropriate.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program is adequate under the relevant EU guideline. These studies were conducted using EU sourced MabThera as the reference product. No data were provided to verify the comparability of the EU sourced and Australian sourced MabThera.
- No meaningful differences between Truxima and MabThera were observed in the comparative pharmacology, pharmacokinetic and toxicity studies.
- The ability of the nonclinical studies to support comparability to Australian MabThera depends on the conclusion regarding the identity of MabThera products across jurisdictions. Provided that EU sourced MabThera is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Truxima.

V. Clinical findings

Introduction

This application is a submission requesting the registration of Truxima/Ritemvia, also referred to by the company development name of CT-P10, which is a biosimilar medicine of rituximab. In this submission, similarity to MabThera (the reference medicinal product in Australia) is claimed. The application for CT-P10 requested approval of the same four treatment indications currently approved for MabThera in Australia, which include non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis and anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)). It is proposed that CT-P10 will be presented in two vial strengths (500 mg and 100 mg) for intravenous (IV) administration, as is currently available for MabThera in Australia.

The submission contains two pivotal Phase III trials, Study CT-P10 3.2 in patients with active rheumatoid arthritis and Study CT-P10 3.3 in patients with advanced follicular lymphoma (AFL). Both of the pivotal Phase III trials are ongoing.[4] The clinical safety and efficacy data up to week 48 and the pharmacokinetic data up to Week 24 in Study CT-P10 3.2 were provided in this submission. Clinical data up to Week 24 (that is, up to core treatment Cycle 8) for Study CT-P10 3.3 was included in this application. In addition, the sponsor has nominated a comparative pharmacokinetic trial in subjects with rheumatoid arthritis (Study CT-P10 1.1) and its open label maintenance phase (Study CT-P10 1.3) as supportive in this submission. Study CT-P10 1.1 randomised 154 patients with rheumatoid arthritis, and had the primary objective of comparing the pharmacokinetic profiles of CT-P10 to EU sourced MabThera. The dossier also included a Phase I pilot study (CT-P10 1.2) with an open label design in patients with relapsed or refractory lymphoma.

[3] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[4] Clarification: Phase I of Study CT-P10 3.2 (24 weeks) was completed in January 2016, Phase II of the study (48 weeks) was ongoing at the time of the first round clinical evaluation.

This trial only enrolled one subject before closing prematurely due to significant patient recruitment issues.

The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) requirements for biosimilar medicines guided the development program for CT-P10. The sponsor is of the opinion that the comparability of CT-P10 to MabThera is representative of the best standards of reference product use, and the label claim for Australia will not significantly depart from that of the Australian Product Information for the reference product, MabThera.

Drug class and therapeutic indication

Rituximab is a chimeric murine/human immunoglobulin (IgG1) monoclonal antibody containing murine light and heavy chain variable region sequences (Fab domain) and human constant region sequences (Fc domain) that bind with high affinity and specificity to the CD20 antigen found on the surface of normal and malignant B-cells in humans.

Rituximab is classified as an antineoplastic agent (in the subgroup of monoclonal antibodies) and has the ATC code of L01XC02. CT-P10 is a monoclonal biosimilar antibody of MabThera, which consists of two kappa light chains and two IgG1 heavy chains. CT-P10 is produced by recombinant DNA technology in a mammalian (Chinese hamster ovary) expression system.

The proposed treatment indications for CT-P10 (Truxima) are identical to the registered treatment indications for the reference product (MabThera) and include:

Non-Hodgkin's Lymphoma

Truxima is indicated for treatment of patients with:

- *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,*
- *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.*

Chronic Lymphocytic Leukaemia

Truxima is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

Truxima (rituximab) 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 at least one tumour necrosis factor (TNF) inhibitor therapy.

Truxima has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

Granulomatosis with polyangiitis and Microscopic polyangiitis

Truxima in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with rituximab have not been established.

Dosage and administration

All of the proposed treatment indications for CT-P10 have a recommended posology consistent with the approved dose regimen for MabThera.

Proposed changes to the product documentation

For CT-P10, the sponsor proposes additions to the currently approved MabThera PI that include short paragraphs in the *Pharmacology, Clinical Trials, Precautions, Adverse Effects* and *Presentation* sections of the PI. The additional detail contains information about the comparability of CT-P10 with MabThera based on the data obtained in the clinical studies included in this submission.

Information on the conditions being treated

Lymphoma

Lymphoma is a malignant disease of the lymphoid system, for which there are two main clinic-pathological types, Hodgkin's disease and NHL. Depending on where it is located in the body NHL can cause different symptoms, but frequent symptoms include painless lymph node enlargement, weight loss and fever with or without infection, pruritus, splenomegaly and fatigue.

The overall incidence of NHL in Australia is 22 cases per 100,000 persons (which is higher in males versus females, 26 versus 18 cases per 100,000, respectively). The mean age at diagnosis is 65.4 years and mortality significantly increases with advancing age. In most cases of NHL, the cause is unknown, but immune system deficiencies (for example, people with HIV or those taking immunosuppressant drugs) and certain infections (for example, Epstein Barr virus infection and human herpes virus 8) are associated with an increased risk of developing NHL. Non-Hodgkin's lymphoma can be classified into indolent (low grade), aggressive (intermediate grade) and very aggressive (high grade) subtypes.

Approximately 40% of new cases of indolent lymphoma are follicular lymphoma, which is the second most common type of NHL worldwide accounting for 20 to25% of all cases. The majority of patients with follicular lymphoma have advanced disease (Ann Arbor stage III or IV) and 50% have bone marrow involvement at diagnosis.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a neoplasm of activated B-lymphocytes, which morphologically resemble mature, small lymphocytes of the peripheral blood, accumulate in the bone marrow, blood, lymph nodes and spleen in large numbers. Patients with CLL present with a wide range of symptoms and signs. Onset is frequently insidious, and it is not unusual for CLL to be discovered incidentally after a blood cell count is performed for another reason (25 to 50% of patients will be asymptomatic at presentation). Enlarged lymph nodes are the most common presenting symptom, seen in 87% of patients symptomatic at time of diagnosis. A predisposition to repeated infections such as pneumonia, herpes simplex and zoster may be noted. Early satiety and/or abdominal discomfort may be related to an enlarged spleen. Muco-cutaneous bleeding and/or petechiae may be due to thrombocytopenia. Tiredness and fatigue may be present secondary to anaemia and 10% of patients with CLL will present with an autoimmune haemolytic anaemia. Transformation of CLL into an aggressive large B-cell lymphoma is seen in approximately 3 to 10% of cases. The incidence of CLL increases with age (usually seen after 50 years of age) and the mean age at diagnosis is 70.0 years (higher in men).

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony

erosion and ultimately loss of function of the affected joints. It is the second most common form of arthritis and the most common autoimmune disease in Australia with a prevalence of 2%. Most patients with rheumatoid arthritis are aged between 35 and 64 years, and women more commonly affected than men (up to 3:1). People with an immediate family history of rheumatoid arthritis have a greater risk of developing the condition and smoking is the most commonly identified lifestyle factor associated with rheumatoid arthritis.

ANCA associated vasculitis

ANCA associated vasculitis is a rare, multisystem, autoimmune disease characterised by small to medium sized vessel vasculitis, the production of ANCA, and a high occurrence for causing significant respiratory tract and kidney disease in its severe form. There are three types of ANCA-associated vasculitis, but the two most common sub-types are GPA and MPA. Both conditions require long term treatment and follow-up as the reported incidence of disease relapse can be as high as 50% at 7 years after diagnosis. The reported incidence of GPA varies from 2 to12 per million of population, and the estimated prevalence varies from 24 to157 per million of population. There is some geographical variation, for example GPA is more common in northern compared to southern European countries.

Although not formally recognised in precise definitions, there are at least two different phenotypes of GPA: systemic/generalised/severe forms (about 2 of 3 of all cases); and localised/limited forms (approximately 1 of 3 of all cases). Systemic GPA is typically characterised by kidney involvement (72 to 80%; usually a necrotising pauci-immune glomerulonephritis), lung disease (65%; nodules and/or pulmonary haemorrhage), systemic features (weight loss and fever) and often involvement of at least 1 other organ (most commonly, the ENT, skin or nervous system). In systemic GPA, approximately 90% of patients have positive serum c-ANCA (diffuse cytoplasmic immunofluorescence pattern) with anti-PR3 (proteinase 3) specificity on further testing.

The incidence of MPA is estimated to be 3 to 24 cases per million of population, and prevalence estimates vary between 25 and 94 per million. MPA has been reported to occur worldwide and can affect all ethnic groups, but with predominance in Caucasian people. Males are affected slightly more frequently (male to female ratio varies from 1.2 to 1.8). The mean age of onset for MPA is 50 years, while GPA typically affects a slightly younger population (mean age of onset 41 years). The most common reported disease manifestations of MPA are renal involvement (nearly 100%; usually a necrotising pauci-immune glomerulonephritis), generalised systemic features (70 to 75%; often myalgia and arthralgia), pulmonary disease (~50%; typically alveolar haemorrhage), gastrointestinal manifestations (~50%; mainly abdominal pain and occasionally bleeding), skin lesions (~50%) and peripheral nervous system involvement (~ 50%; usually mononeuritis multiplex). Positive ANCA serology is detected in 2 of 3 of cases, with the major observed pattern being p-ANCA (perinuclear staining) with anti-MPO (myeloperoxidase) specificity.

Current treatment options

Non-Hodgkin's lymphoma

Treatment for NHL depends on the subtype of lymphoma, stage of disease and the expected rate of disease progression. Current treatment options for NHL in Australia include chemotherapy and radiotherapy, alone or in combination. Alkylator based combination chemotherapy with cyclophosphamide has been the standard first line treatment option for patients with advanced indolent lymphoma for 20 years, but in the last 10 years there is published evidence showing improved overall survival (OS) rates with the addition of rituximab to combination chemotherapy with cyclophosphamide, vincristine and prednisone (CVP) versus CVP alone (4 year overall survival of 83% versus

77%).[5] Moreover, the introduction of rituximab maintenance treatment after successful induction treatment with chemotherapy has increased progression free survival rates.[6] Therefore, at present, the recommended treatment for advanced follicular lymphoma (that is, the population enrolled in Study CT-P10 3.3) involves the use of rituximab in combination with chemotherapy for induction treatment followed by rituximab maintenance therapy.

Chronic lymphocytic leukaemia

Treatment for CLL depends on the stage of disease and the expected rate of disease progression. Current treatment options for CLL in Australia include chemotherapy with fludarabine and alkylating agents such as cyclophosphamide. Glucocorticoids are also useful in certain circumstances such as in the treatment of associated Coombs positive haemolytic anaemia and immune thrombocytopenia. Radiotherapy may occasionally be useful in palliating localised disease or hypersplenism in the aged. Monoclonal antibodies such as rituximab may be one of the treatment options along with chemotherapy in younger patients with poor prognostic factors such as very high lymphocyte cell numbers or rapid doubling time. An autologous stem cell transplant may also be one of the treatment options in selected cases.

Rheumatoid arthritis

Rheumatoid arthritis is a heterogeneous condition in terms of clinical presentation, natural history and drug responsiveness. Published evidence and current guidelines for the treatment of rheumatoid arthritis emphasise the importance of achieving clinical remission, or at least low disease activity, as both of these states are associated with a favourable long term prognosis. In addition to treating the signs and symptoms of rheumatoid arthritis, an impact on inhibiting the structural bone damage of the condition is highly desirable as this is associated with better long-term patient outcomes, particularly regarding maintenance of physical function and quality of life.

Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs, in particular, methotrexate (MTX)), alone or in combination with each other, are the initial recommended treatments for rheumatoid arthritis. Observational studies and meta-analyses of DMARD treatment efficacy and tolerability demonstrate highly variable outcomes to single and combination DMARD therapy over time. In 10 year follow-up studies, 25% of patients with rheumatoid arthritis had to discontinue conventional DMARD treatment due to insufficient therapeutic benefit and 20% discontinued treatment due to adverse effects.

Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active rheumatoid arthritis after conventional synthetic DMARD failure or intolerability. While anti-TNF drugs and cytokine modulators such as abatacept and tocilizumab have been shown to demonstrate significant efficacy in treating active rheumatoid arthritis, a substantial proportion of patients do not achieve meaningful American College of Rheumatology (ACR) responses. Based on the current literature for biological therapies, ACR20 response rates range from 50 to 65% and ACR50 response rates are 35 to 50%. So despite the availability of many therapies with various modes of action for the treatment of rheumatoid arthritis, a significant proportion of individuals either fail to initially respond to treatment, do not tolerate therapy or lose response over time. Rituximab is approved in Australia and around the world for the treatment of active

[5] Marcus R, et al., Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma, *J Clin Oncol*. 2008; 26: 4579-4586
[6] Salles Get al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase III, randomised controlled trial, *Lancet.* 2011; 377: 42-51 Erratum in: *Lancet.* 2011; 377:1154

rheumatoid arthritis in patients who have an inadequate response to at least one anti-TNF therapy.

ANCA associated vasculitis

Patients with GPA and MPA typically have systemic disease at presentation (few have limited disease) and receive induction treatment with high dose IV glucocorticoids together with cyclophosphamide. Rituximab is an approved alternative induction treatment for severely active GPA and MPA. However, the efficacy and safety of re-treatment with rituximab has not been established. After induction of remission treatment, patients with GPA and MPA are recommended to receive maintenance therapy for at least 2 years, which may include the drug options of azathioprine, methotrexate or mycophenolate in conjunction with low dose oral glucocorticoids. Although there is some published evidence to suggest that rituximab may be a useful alternative in the maintenance of GPA remission, this is not an approved treatment indication for the reference product MabThera.[7]

Evaluator's commentary on the background information

CT-P10 is a biosimilar medicine of rituximab proposed for registration in Australia. Other complex biological drugs (in particular, the anti-TNF medicines of infliximab and etanercept) already have biosimilar therapies approved in Australia, both of which have been granted the full list of treatment indications of the originator biologic medicine. CT-P10 is given by IV infusion and primarily exerts its oncology and immunomodulatory effects via B-cell lysis. In all of the clinical treatment conditions, there are several potential downstream effects of B-cell lysis including reduced activation of T-lymphocytes, decreased auto-antibody production in several autoimmune diseases and sensitisation of lymphoma cells to conventional chemotherapeutic drugs.

In general, the sponsor has adhered to the TGA guidelines on the registration of a biosimilar medicine in this submission. Moreover, the sponsor has provided information on the overseas regulatory status of CT-P10. In particular, the sponsor has included the CHMP evaluation report with a positive recommendation for registration in the EU in this submission. The sponsor has appropriately justified the formulation development program for CT-P10. Some of the key issues to consider in this submission are common to biosimilar medicine applications. The sponsor needs to demonstrate that CT-P10 results in clinical effects (efficacy and safety outcomes) that are comparable to the Australian reference product, MabThera. In addition, to make a claim of treatment indication extrapolation the sponsor needs to articulate that the therapeutic efficacy of rituximab relies on a similar mechanism of action in the extrapolated indications. Furthermore, the biosimilar therapy needs to demonstrate equivalence with the reference drug for pharmacokinetic (pharmacokinetic) parameters as well as immunogenicity (mainly, rates and types of anti-drug antibody formation). However, lower rates of immunogenicity with the biosimilar may be acceptable.

Clinical rationale

Rituximab is a recombinant chimeric murine/human monoclonal antibody directed against the cluster of differentiation 20 (CD20) antigen, a hydrophobic transmembrane protein located on the surface of normal pre-B-lymphocytes and mature B-lymphocytes. Following binding, rituximab triggers a host cytotoxic immune response against CD20 positive cells, which are important in the pathogenesis of lymphoid malignancies and

[7] Guillevin L, et al.; French Vasculitis Study Group., Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis., *N Engl J Med*. 2014; 371: 1771-1780

certain autoimmune diseases, particularly, active rheumatoid arthritis and ANCA associated vasculitis. MabThera is currently approved in Australia for use in four treatment indications. The central therapeutic effect of MabThera in all these indications is mediated by the depletion of B-lymphocytes and the subsequent effects on the immune system including reduced activation of T-lymphocytes and changes in cytokine profiles. Reducing disease activity and burden, as well as slowing the progression of lymphoid malignancy and inflammatory disease are key therapeutic goals. MabThera is well established and widely used in Australian adult haematology and rheumatology clinical practice for more than10 years and has a well-characterised benefit: risk profile.

Formulation development

Pre-clinical

The development of CT-P10 and the demonstration of biosimilarity between CT-P10 and EU-MabThera (produced by Roche, Switzerland) are consistent with the EU guidelines regarding the scientific principles of a biosimilar comparability exercise using the step-wise approach (as recommended by the EMA's Committee for Medicinal Products for Human Use (CHMP)). As part of the quality development program, a diverse range of orthogonal and highly sensitive methods were used to assess biosimilarity between CT-P10 and reference rituximab products.

The similarity of CT-P10 to reference products (EU-MabThera and US-Rituxan (produced by Genentech, USA)) was first established by extensive physicochemical characterisation to confirm similar primary order, secondary order and higher order structure, as well as post-translation modifications and the glycosylation profile. Secondly, the sponsor demonstrated that the biological activity of CT-P10 is highly similar to reference rituximab regarding CD20 and Fc gamma receptor binding affinities, as well as for CDC, ADCC and apoptotic activities.

Finally, the biological activity of CT-P10 and reference rituximab drugs has been directly compared using primary cells isolated from healthy donors, and also in patients with NHL and CLL. The results of the quality studies established that CT-P10 and EU-MabThera / US-Rituxan are highly similar in physical and chemical attributes, as well as all biological activities associated with rituximab. The non-clinical evaluation report covered these issues in detail and is required to support the validity of the clinical evidence for the claim of biosimilarity between CT-P10 and EU-MabThera.

Bridging comparability between EU and Australian MabThera

In support of this application, the sponsor also performed supplemental comparability (bridging) studies that demonstrated equivalence between EU-sourced MabThera and Australian sourced MabThera. The in vitro comparability testing items and parameters were in accordance with TGA advice during the submission planning phase. Overall, the bridging study indicated comparability with respect to primary and higher order structure, modification and post-translational forms, biological activity, purity/impurities and content between EU- MabThera and Australian MabThera.

Clinical program

The formulation development process for CT-P10 was initiated in 2009 and designed to replicate the reference product (MabThera/Rituxan) from a quality and clinical perspective. The same formulation of CT-P10 was consistently used throughout the development process. The quality attributes of CT-P10 drug products produced by development processes have been assessed in a comparability study and no significant differences in drug formulation were found. During the Phase III clinical studies the drug substance and drug product manufacturing processes were further refined to generate a commercial process, which demonstrated comparability with earlier development

processes. CT-P10 drug product manufactured using the commercial process was used in the Phase III clinical studies, which are ongoing. Extensive comparability studies have been conducted to confirm that the changes to the manufacturing process had no impact on the quality of the CT-P10 drug substance and product.

The excipients of CT-P10 are similar to the reference product MabThera (as recorded in the Australian PI for the 100 mg and 500 mg vial presentations).

Guidance

The TGA recommended the following guidance documents to the clinical evaluator for consideration:

- Therapeutic Goods Administration: Regulation of biosimilar medicines (version 2.0; December 2015).
- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007
- CHMP/437/04/Rev 1: Guideline on Similar Biological Medicinal Products. Effective: 25 May 2015
- EMA/CHMP/BMWP/86289/2010: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. Effective: 1 June 2014
- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues. Effective: 17 August 2015

Contents of the clinical dossier

The clinical dossier contains two pivotal Phase III trials, Study CT-P10 3.2 in patients with active rheumatoid arthritis and Study CT-P10 3.3 in patients with advanced follicular lymphoma, both of which are ongoing. Part 1 of Study CT-P10 3.2 aimed to compare the pharmacology, safety and tolerability of three different formulations of rituximab (CT-P10, EU sourced MabThera and US sourced Rituxan) in 189 adult patients with active rheumatoid arthritis. Part 2 of Study CT-P10 3.2 continued to collect clinical and pharmacokinetic equivalence data for CT-P10 and Rituxan.

Equivalence pharmacokinetic and clinical data (efficacy and safety) between CT-P10 and Rituxan was examined in an oncology indication in Study CT-P10 3.3. The clinical program had the objective of achieving regulatory guidelines for the demonstration of biosimilarity between CT-P10 and the approved Australian reference product, MabThera. The clinical dossier also contained three additional trials:

- Study CT-P10 1.1 was a randomised Phase I trial with the primary objective of demonstrating the pharmacokinetic equivalence of CT-P10 and MabThera in patients with active rheumatoid arthritis;
- Study CT-P10 1.3; an open label, maintenance phase extension trial that aimed to assess the longer term efficacy and safety of CT-P10 in patients with rheumatoid arthritis.
- Study CT-P10 1.2 was an open label, single-arm, pilot Phase I trial of CT-P10 in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), which is an aggressive subtype of NHL.

The submission contained the following clinical information:

- One pivotal clinical pharmacology study (Part 1 of Study CT-P10 3.2) in adults with active rheumatoid arthritis that aimed to demonstrate the 3-way pharmacokinetic equivalence between CT-P10, EU sourced MabThera and US sourced Rituxan.
- Supporting pharmacokinetic equivalence data between CT-P10 and Rituxan was examined in Part 1 of Study CT-P10 3.3 (oncology population – advanced follicular lymphoma), and between CT-P10 and MabThera in Study CT-P10 1.1 (rheumatoid arthritis patients).
- No dose finding studies or population pharmacokinetic analyses.
- The key pharmacodynamic endpoint of B-cell kinetics including depletion and recovery was evaluated in four of the submitted clinical studies (recommended by the EMA).
- One pivotal Phase III, efficacy/safety study (CT-P10 3.2) in patients with active rheumatoid arthritis. Clinical and pharmacokinetic data up to Week 48 was provided in this submission.
- One pivotal Phase I/III, efficacy/safety study (CT-P10 3.3) in patients with advanced follicular lymphoma. Clinical data up to Week 24 (8 core treatment cycles) was provided.
- One supporting open label, maintenance treatment trial in subjects with rheumatoid arthritis (Study CT-P10 1.3) that provided clinical and pharmacodynamic data for up to 24 weeks in the extension phase.
- One supporting open label, single arm, pilot Phase I trial of CT-P10 in patients (with only 1 subject enrolled) with relapsed or refractory DLBCL.
- The submission also contained a Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Biopharmaceutical Studies and associated Analytical Methods, Summary of Clinical Pharmacology Studies, Position Paper on Extrapolation of the role of B-lymphocytes in health and disease,
- Literature references.

Paediatric data

The submission did not include any paediatric specific data, which is appropriate given the target populations in the requested treatment indications for CT-P10.

Good clinical practice

The design, conduct and analysis of all of the clinical studies provided in this submission for CT-P10 were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met. There were two GCP non-compliant sites (one in Study CT-P10 3.2 and one in Study CT-P10 3.3) identified by the contract research organisation, which were closed due to scientific misconduct and serious GCP non-compliance. The patients enrolled at these sites were excluded from all analysis populations, but included in sensitivity analyses for the primary pharmacokinetic endpoint of Study CT-P10 3.3 and serious adverse events (SAEs) of Study CT-P10 3.2.

Evaluator's commentary on the clinical dossier

The sponsor designed the clinical development program for CT-P10 to demonstrate equivalent safety, efficacy and pharmacokinetic outcomes to the appropriate reference product, MabThera. The dossier includes five clinical trials including two pivotal randomised, multi-centre, double blind, and Phase III studies in two different treatment

indications (rheumatoid arthritis and NHL). Study CT-P10 3.2 evaluated the comparative efficacy, safety and pharmacokinetic of CT-P10, EU sourced MabThera and US sourced Rituxan in an active rheumatoid arthritis population setting, which required the addition of rituximab to low dose weekly methotrexate in patients with an inadequate response to at least one anti-TNF therapy. Study CT-P10 3.3 examined the pharmacokinetic and clinical equivalence of CT-P10 and Rituxan in patients with advanced follicular lymphoma. Additional Phase I studies in rheumatoid arthritis (Studies CT-P10 1.1 and 1.3) and DLBCL (Study CT-P10 1.2) were conducted to assess the efficacy, safety and pharmacokinetic profiles of CT-P10 to other formulations of rituximab. Clinical study reports were provided for each trial and the safety data was presented by individual study, as well by pooled datasets (by treatment indication) for adverse events of special interest (such as infusion related reactions, cytopaenias and infections).

Although two sites in the Phase III program were identified to be GCP non-compliant, the overall datasets have not been compromised by the exclusion of information from the GCP non-compliant sites. The submission also included a comprehensive Position Paper on Extrapolation of the role of B-cells in health and disease, pharmacokinetic-pharmacodynamic, bio-distribution and immunogenicity data. In general, the data in the submission was well presented. Moreover, several of the studies had complicated designs (for example, two parts with patient roll-over and differing dosing strategies for rituximab re-treatment that made it complex to understand results).

The clinical development program for CT-P10 has two specific issues that need to be considered. Firstly, rheumatoid arthritis and advanced follicular lymphoma (subtype of NHL) are the only two disease conditions in which CT-P10 has been rigorously studied, and careful reflection about the sensitivity of the efficacy measures and diseases in both of the pivotal Phase III studies is required with respect to extrapolation of treatment indication. Secondly, the submitted dataset contains very limited information about treatment switches between the rituximab formulations (only currently available for 20 adult subjects with rheumatoid arthritis treated in Study CT-P10 1.3).

Pharmacokinetics

Studies providing pharmacokinetic data

In accordance with the relevant TGA adopted EU guidelines; [8] [9] the clinical dossier presented a total of three studies for demonstrating similarity in pharmacokinetic characteristics between CT-P10 and originator rituximab formulations (MabThera and Rituxan).

The Phase I Study CT-P10 1.1 in adult patients with rheumatoid arthritis receiving concomitant low dose weekly methotrexate had the primary objective of demonstrating the pharmacokinetic equivalence of CT-P10 and MabThera up to 24 weeks, but the trial continued to collect pharmacokinetic data up to 72 weeks as a secondary and tertiary objective. Part 1 of the Phase III Study CT-P10 3.2 in subjects with rheumatoid arthritis had pharmacokinetic endpoints as a co-primary objective of the trial and aimed to demonstrate the pharmacokinetic equivalence of CT-P10 with MabThera (EU sourced) and Rituxan (US sourced) over the first 24 weeks of therapy. The third pharmacokinetic study included in the submission was conducted in an oncology treatment population. Study CT-P10 3.3 was a Phase III trial in subjects with advanced follicular lymphoma and

[8] EMA/CHMP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
[9] EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products 5 containing monoclonal antibodies

had the co-primary objective of demonstrating the pharmacokinetic equivalence of CT-P10 with Rituxan at Cycle 4 (Weeks 9 to12) of the core study period. None of the studies had significant deficiencies that excluded their results from consideration. The CT-P10 development program does not include any studies conducted in healthy volunteers, which is appropriate given the potential toxicity of rituximab.

Evaluator's conclusions on pharmacokinetics

The comparative pharmacokinetics characteristics of CT-P10 and the approved reference drugs (EU-MabThera and US-Rituxan) were investigated in three clinical trials.

The Phase I Study CT-P10 1.1 was specifically designed to evaluate the pharmacokinetics of CT-P10 in subjects with rheumatoid arthritis aged between 18 and 75 years, and to demonstrate the pharmacokinetics equivalence of CT-P10 with MabThera for the co-primary endpoints of area under the curve (AUC) from dosing to last measurable concentration ($AUC_{0\text{-last}}$) and maximum concentration (C_{max}). These co-primary pharmacokinetics endpoints are appropriate for demonstrating pharmacokinetics similarity. It was agreed with the EMA and FDA to determine pharmacokinetics equivalence using a single course of rituximab (two 1000 mg doses given 2 weeks apart) for which $AUC_{0\text{-last}}$ and C_{max} would lie within the pre-determined equivalence margin of 80 to 125%. This was observed to be correct for Study CT-P10 1.1, in which CT-P10 was demonstrated to have geometric least squares means ratios compared to MabThera close to 100% (and always within the 80 to 125% equivalence margin) for both primary pharmacokinetics endpoints. Study CT-P10 1.1 also demonstrated that CT-P10 was bioequivalent with the appropriate reference product (MabThera) for a range of secondary pharmacokinetics parameters including AUC over different time frames (up to 24 weeks), T_{max}, $T_{½}$, drug clearance (CL) and apparent volume of distribution (Vd).

Part 1 of Study CT-P10 3.2 was a three-arm, Phase III trial in adult patients with active rheumatoid arthritis that also demonstrated that CT-P10 was equivalent to EU sourced MabThera and US sourced Rituxan for various pharmacokinetics endpoints. For the primary pharmacokinetics measures of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} after the second infusion, CT-P10 was able to achieve similar drug concentrations of rituximab up to Week 24. In addition, all of the secondary pharmacokinetics outcomes (both in Part 1 and Part 2) showed equivalence between CT-P10 and reference rituximab products. However, all three formulations of rituximab exhibited moderate inter-patient variability in drug exposure with the CV% for serum AUC values ranging from 25.9 to 34.7% for CT-P10 and 23.5 to 35.6% for reference rituximab drugs.

Study CT-P10 3.3 was the third study in this submission that collected pharmacokinetics data and the primary objective of Part 1 was to demonstrate the pharmacokinetics equivalence of CT-P10 and Rituxan in an oncology treatment population (advanced follicular lymphoma). Part 1 of the trial enrolled a total of 121 subjects and the primary pharmacokinetics endpoints were AUC_{tau} and C_{max} at steady state (at core Cycle 4 Weeks 9 to 12). This study also demonstrated the pharmacokinetics equivalence of CT-P10 and Rituxan for a range of primary and secondary pharmacokinetics parameters.

All three of the studies showed mean serum concentration-time profile data for CT-P10 consistent with the known pharmacokinetics characteristics of rituximab. After IV administration, rituximab binds to CD20 antigen present on the surface of normal or neoplastic B-cells in the peripheral blood, bone marrow and lymph nodes. After systemic distribution, there are different mechanisms of transport through capillary endothelial cells and into tissues. The volume of distribution of rituximab at steady state is approximately 6 L, which suggests some distribution of drug into the extracellular spaces, except the central nervous system. The drug is slowly cleared from the body with the mean $T_{½}$ ranging from 17 to 32 days. All three of the studies examined for the effect of

anti-drug antibodies (anti-drug antibodies) upon the pharmacokinetics of rituximab and the two rheumatoid arthritis trials showed a reduced drug exposure in anti-drug antibodies positive subjects (up to 24 weeks) for all rituximab formulations, particularly MabThera therapy in Study CT-P10 3.2. The sponsor did not present the pharmacokinetics data by medium to high positive titres of anti-drug antibodies, which may further elucidate this issue.

The clinical dossier for CT-P10 contained pharmacokinetics assessments collected in > 300 adult patients with active rheumatoid arthritis and > 100 subjects with advanced follicular lymphoma (that is, 2 of the 4 approved treatment indications for rituximab). In the submission, the sponsor also provided an overview of the pharmacokinetics characteristics of rituximab by treatment indication and reported significant pharmacokinetics similarity between the claimed treatment indications, albeit the different approved dose regimens in a heterogeneous group of condition (that is, fixed dose regimen in rheumatoid arthritis and body surface area guided posology in NHL, CLL and ANCA associated vasculitis). As such, no significant pharmacokinetics differences between CT-P10 and reference rituximab drugs should be expected for the other claimed treatment indications.

Overall, the pharmacokinetics assessments provided in this submission for the registration of CT-P10 as a biosimilar product of MabThera and Rituxan are appropriate, and the data largely meets the minimum criteria of supporting evidence for pharmacokinetics bioequivalence.

Pharmacodynamics

Studies providing pharmacodynamic data

In accordance with the relevant TGA adopted EU guidelines;[10,11] the submission presented a total of four studies for demonstrating similarity in pharmacodynamic characteristics between CT-P10 and originator rituximab formulations (MabThera and Rituxan). The Phase I Study CT-P10 1.1 in adult patients with rheumatoid arthritis receiving concomitant low dose weekly methotrexate had the secondary objective of examining the pharmacodynamic effects of CT-P10 compared to MabThera for up to 72 weeks of treatment follow-up. Study CT-P10 1.3 was an open label, single-arm extension trial of Study CT-P10 1.1 in which the long-term safety (including B-cell kinetics) of CT-P10 was investigated. The Phase III Study CT-P10 3.2 in subjects with rheumatoid arthritis collected pharmacodynamic data up to Week 48 as a pre-specified secondary objective. Study CT-P10 3.3 in patients with advanced follicular lymphoma also had the secondary objective of evaluating the B-cell kinetics of CT-P10 and Rituxan up to core Cycle 8 of therapy (24 weeks). None of the studies had significant deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The sponsor has appropriately nominated B-cell depletion and recovery as the principal, clinically relevant pharmacodynamic markers of the therapeutic activity of rituximab. As such, B-cell counts over time as measured by validated assays were selected as the key pharmacodynamic endpoint for the assessment of pharmacodynamic similarity between CT-P10 and reference rituximab drugs. However, it must be noted that there is no strong

[10] EMA/CHMP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
[11] EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products 5 containing monoclonal antibodies

correlation between the extent of B-cell reduction, and the magnitude of the clinical efficacy response in rheumatoid arthritis and NHL.

In Study CT-P10 1.1, mean B-cell levels below the lower limit of quantitation (20 cells/µL) were reached at the end of infusion in the CT-P10 arm. In the MabThera group, all but 1 subject had reached levels < 20 cells/µL within 15 minutes after the end of the infusion. In both treatment groups, B-cell counts consistently remained < 20 cells/µL until Week 16 for the vast majority of patients. B-cell recovery is likely to be the most sensitive pharmacodynamic endpoint available. Available data from Study CT-P10 1.1, that is, the composite outcome of the need for earlier re-treatment (58% in the CT-P10 arm versus 45% in the MabThera group) and earlier B-cell recovery in the remaining patients of the CT-P10 arm (as shown in Table 3), appears to be suggestive of a relevant difference in the duration of action of the two rituximab drugs, which would not be favourable for CT-P10.

The sponsor is aware of this observation in Study CT-P10 1.1 but reports that the relatively shortened duration of activity with CT-P10 versus MabThera is likely to be a chance finding for several reasons including the 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 (lower limit of quantitation (LLOQ) of 20 cells/µL) versus highly sensitive flow cytometry that can currently detect levels as low as 0.1 cells/µL (and therefore may allow better correlation between B-cell depletion and clinical response); and the trial was small and only numerical trends were observed (that is, no statistical confirmation), especially since individual responses following rituximab therapy are known to be highly variable.

Table 3: Patients achieving B-cell recovery in the core period of Study CT-P10 1.1

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%)

In contrast to Study CT-P10 1.1, Study CT-P10 3.2 was designed with systematic re-treatment with rituximab at Weeks 24 and 26 (except for safety reasons which occurred in 4 patients; 1% of all subjects). Due to this design, little additional information is available to assess the duration of B-cell response. The B-cell kinetics observed in Study CT-P10 3.2 showed that B-cell counts decreased to below the LLOQ (20 cells/µL) immediately after the first infusion for all patients except 1 subject in CT-P10 group, and then remained below this level up to Week 24 in the majority of patients (~96%) in all treatment groups. Nevertheless, the analysis of Part 1 showed a trend for earlier B-cell recovery with CT-P10 and Rituxan compared to MabThera, which is the Australian approved reference rituximab. While the proportion of patients with B-cell recovery before Week 48 was higher with Rituxan than CT-P10, 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. When the pharmacodynamic data from Parts 1 and 2 of the study were combined, a slight difference between the two cohorts (CT-P10 and reference products) was apparent after the first treatment course for B-cell recovery. After the second treatment course, early B-cell recovery was infrequent, regardless of which rituximab drug used.

Additional pharmacodynamic and efficacy analyses for both rheumatoid arthritis trials, including a time to event Kaplan-Meier analysis with the event being first B-cell value above the lower limit of quantitation 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 may need more frequent drug administrations.

In Study CT-P10 3.3 (patients with advanced follicular lymphoma), the extent of B-cell depletion appears similar between the two treatment arms (CT-P10 and Rituxan) up to 24 weeks of therapy. The pattern (that is, magnitude of titre change from baseline and time course to onset) of treatment related changes in disease associated pharmacodynamic outcomes such as C-reactive protein (CRP), eosinophil sedimentation rate (ESR), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody levels were similar between CT-P10 and MabThera in the rheumatoid arthritis treatment studies CT-P10 1.1 and CT-P10 3.2.

In conclusion, the submission contains a sufficient quantity of robust data to support the claim of biosimilarity for CT-P10 and reference rituximab drugs from a pharmacodynamic perspective.

Dosage selection for the pivotal studies

Consistent with a biosimilar drug submission, the doses and regimens of rituximab selected for investigation in the CT-P10 clinical study program (adult patients with active rheumatoid arthritis or lymphoma) was based on the posology used in the reference drug registration trials and it's approved PI.

In the two randomised trials involving adult patients with active rheumatoid arthritis (Studies CT-P10 1.1 and CT-P10 3.2), rituximab was given by IV infusion with a fixed dose posology (two 1000 mg doses, given 2 weeks apart), which defined a single course of treatment. Subjects with rheumatoid arthritis were eligible to receive repeat courses of rituximab in Study CT-P10 1.1 if there was documented evidence of disease relapse and safety parameters were met. However, in Study CT-P10 3.2, re-treatment with rituximab was systematically administered at Weeks 24 and 26 (that is, at 6 months) in responding subjects who met safety parameters for re-dosing. In rheumatoid arthritis, 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 Summary of Product Characteristics for MabThera (rheumatoid arthritis indication), but rather based on return of disease activity in order to avoid potential over-treatment and to decrease infection risks. In the Australian PI for MabThera, it is recommended that rheumatoid arthritis patients may receive further courses of rituximab based on the signs and symptoms of disease, and that no patient should receive another course of MabThera within 16 weeks of a previous treatment course.

In both of the rheumatoid arthritis studies, rituximab was co-administered with methotrexate 7.5 or 10 to 25 mg/week and folic acid (at least 5 mg/week). Overall, the use of rituximab in the CT-P10 rheumatoid arthritis studies is consistent with clinical practice in Australia. Subjects were to receive their IV infusion of rituximab in accordance with the approved PI, which required pre-medication with 100 mg of IV methylprednisolone at least 30 minutes prior to each infusion as well as anti-pyretic (usually paracetamol) and

anti-histamine drugs. The rates of infusion were also consistent with the approved PI for rituximab.

The reference drugs used in the pivotal Phase III rheumatoid arthritis Study CT-P10 3.2 were EU sourced MabThera (Part 1 only) and US sourced Rituxan (both study parts). Australian sourced (AU) MabThera has been compared with EU MabThera with respect to quality attributes and based on this analysis, the sponsor asserts that the comparability of Australian sourced MabThera and EU MabThera has been demonstrated, and therefore it is justifiable to use EU MabThera as the nominated reference product. The sponsor has provided a bridging comparability study between three batches of Australian MabThera and one batch of EU MabThera, and concluded that their physicochemical and biological properties were within pre-defined similarity ranges. The opinion of the non-clinical evaluator with respect to the comparability of Australian and EU sourced MabThera for quality attributes will be crucial to the claim of biosimilarity.

In the pivotal Phase I/III oncology trial (Study CT-P10 3.3), which evaluated adult patients with advanced follicular lymphoma, the investigated posology of rituximab was based on body surface area calculations at the currently approved posology for reference rituximab of 375 mg/m^2 on Day 1 of each treatment cycle. The report for Study CT-P10 3.3 contained data for up to 8 treatment cycles (with each Cycle being a minimum of 21 days duration). Subjects received concurrent conventional chemotherapy with cyclophosphamide, vincristine and prednisolone, which is appropriate concomitant therapy for the treatment indication.

The rituximab reference drug in Study CT-P10 3.3 was US sourced Rituxan. For justification of the chosen comparator rituximab therapy in this study, the applicant asserted that the reference drug link between US Rituxan and AU MabThera was based on it demonstrating 3-way pharmacokinetics equivalence between CT-P10 and MabThera, CT-P10 and Rituxan, and MabThera and Rituxan in 189 rheumatoid arthritis patients in Part 1 of Study CT-P10 3.2. The sponsor believes this data established a robust scientific bridge between these three rituximab products. Therefore, either MabThera or Rituxan could be used as a comparator in subsequent studies and the clinical therapeutic equivalence data generated with CT-P10 can be reliably compared with those from the combined the reference products (MabThera + Rituxan) in Part 2 of Study CT-P10 3.2, as well as the supportive pharmacokinetics equivalence data between CT-P10 and Rituxan in an oncology indication (Part 1 of Study CT-P10 3.3).

Efficacy

Studies providing efficacy data

The submission contains two pivotal Phase III trials: Study CT-P10 3.2 in adult patients with active rheumatoid arthritis and Study CT-P10 3.3 in subjects with advanced follicular lymphoma. For supportive efficacy purposes, the sponsor has also provided a Phase I trial (Study CT-P10 1.1) conducted in patients with active rheumatoid arthritis and its ensuing open label, treatment extension phase (Study CT-P10 1.3). The sponsor has provided a literature review to support the proposed extrapolation to all other approved treatment indications for MabThera to CT-P10.

Evaluator commentary

Study CT-P10 3.2 was a two part, Phase III trial conducted in adult patients with active rheumatoid arthritis that was inadequately responsive to (or intolerant of) prior or current anti-TNF therapy, as well as current low dose weekly methotrexate. The trial randomised a total of 372 patients (161 of whom received CT-P10 and 211 subjects received reference rituximab treatment) and provided efficacy data for up to 24 weeks of

therapy. The pivotal study was well designed, had an appropriate primary efficacy endpoint (mean change from baseline to Week 24 in Disease activity score (DAS28)-CRP score) and had a suitable pre-specified statistical analysis plan that was appropriately powered for the stated equivalence margin. The pre-defined equivalence margin of ± 0.6 change in the DAS28 score is consistent with the validated upper limit of acceptability for this outcome measure, and the sponsor has adequately justified that margin as being congruent with CHMP recommendations.

In general, Study CT-P10 3.2 recruited patients with established rheumatoid arthritis (overall mean duration of approximately 10 years) with the appropriate demographic and disease activity characteristics at baseline. All but 2 subjects had previously received anti-TNF therapy. During Study CT-P10 3.2, all patients continued to receive background weekly methotrexate at a mean dose of approximately 15 mg, which is similar to what is reported with other biologic DMARD trials and is consistent with Australian clinical practise for rheumatoid arthritis patients receiving rituximab. Out of 372 randomised patients, a total of 345 (92.7%) patients completed the first treatment course: 145 (90.1%) patients in the CT-P10 group and 200 (94.8%) subjects in the reference arm. The rate of discontinuation with the first rituximab treatment course was higher in the CT-P10 group (9.9%; 16 of 161) compared with the reference drug arm (5.2%; 11 of 211). The two most frequently reported reasons for discontinuation in both treatment cohorts during the first course were withdrawal of patient consent and adverse events.

In Study CT-P10 3.2, CT-P10 and reference rituximab drugs (MabThera and Rituxan) demonstrated similar clinical outcomes for the primary efficacy endpoint of the mean change from baseline to Week 24 in the DAS28-CRP score. This outcome was shown in both the efficacy population (-2.14 for CT-P10 versus -2.09 for reference rituximab) as well as in the all randomised population (-2.13 for CT-P10 versus -2.09 for reference therapy). The estimated treatment difference was -0.05 for the efficacy population and the 95% CI (-0.29 to 0.20) was fully contained within the predefined equivalence margin of -0.6 to +0.6, thereby supporting the therapeutic equivalence of CT-P10 to the reference rituximab products. A significant supporting analysis of the primary efficacy endpoint was the mean change from baseline in disease activity as measured by DAS28-ESR score up to Week 24. The adjusted mean change in DAS28-ESR for the efficacy population was -2.41 in the CT-P10 group and -2.35 in the reference products arm, with the estimated treatment difference being -0.06 (95% CI -0.31 to 0.19). This result supports therapeutic equivalence between the two treatment cohorts.

Subgroup analyses of the primary efficacy endpoint by patient factors of interest were also performed. The mean changes from baseline to Week 24 in DAS28-CRP score (using the efficacy population) were equivalent between the two treatment groups regardless of anti-drug antibody status (positive/negative), and for patients with at least 8 tender and swollen joints at baseline. The presence of anti-drug antibodies to reference rituximab drugs resulted in a numerically lower mean decrease from baseline in DAS28-CRP score at 24 weeks (-2.0 versus -2.3 to -2.4 for all other subgroups).

Similar efficacy between the two treatment groups in Study CT-P10 3.2 could also be shown for all secondary efficacy endpoints including the American College of Rheumatology scores (ACR) 20, ACR50 and ACR70 responses rate at Week 24, as well as the European League Against Rheumatism (EULAR) response criteria and mean changes from baseline in Clinical disease activity index (CDAI) and Simplified disease activity index (SDAI). In addition, the time response curves for CT-P10 and reference rituximab drugs up to Week 24 were estimated to be equivalent, which is a significant supporting analysis as potential differences in efficacy are more likely to be detected during the rapid rise phase of the time response curve compared with the later plateau phase[12]. However, Study CT-

[12] Kay J and Isaacs JD. Clinical Trials of biosimilars should become more similar. *Ann Rheum Dis* 2017; 76: 4-6

P10 3.2 did not assess structural x-ray outcomes in rheumatoid arthritis, which is a minor deficiency of its design.

The comparison of the primary endpoint result (that is, mean change from baseline in DAS28-CRP score at Week 24) of Study CT-P10 3.2 with the published data for rituximab (REFLEX and DANCER studies) shows a slightly greater mean improvement from baseline in DAS28-CRP score for patients treated in Study CT-P10 3.2 (-2.1) than the originator rituximab drug trials (-1.9 to -2.0). Likewise, when comparing the Week 24 ACR20 response rates observed in Study CT-P10 3.2 (73.5 to 75.9%) with the results of the REFLEX and DANCER trials (51 to 52%), the rates of ACR20 response are significantly higher than expectations.

Between Weeks 24 and 48 of Study CT-P10 3.2, patients (most of whom were re-treated with a second course of rituximab) demonstrated maintenance of treatment response. The mean decreases from baseline in DAS28 score (using either CRP or ESR) remained statistically and clinically significant (ranging from -2.6 to -3.1) at all assessed time points (Weeks 32, 40 and 48). Moreover, the rates of ACR response between Weeks 24 and 48 were maintained in both treatment cohorts between Weeks 24 and 48 following a second rituximab treatment course.

Overall, the efficacy data recorded up to Week 48 in Study CT-P10 3.2 is sufficient to establish therapeutic equivalence between CT-P10 and reference rituximab products for the treatment indication of adult patients with active rheumatoid arthritis. The trial complied with most aspects of the TGA adopted guideline;[13] for the assessment of rheumatoid arthritis. In particular, the trials design, clinical efficacy outcomes, overall number of evaluated subjects and the duration of drug exposure meet the minimum standards outlined in the guidance document.

Other efficacy studies for rheumatoid arthritis indication

Evaluator commentary

Study CT-P10 1.1 was a Phase I clinical trial primarily designed to demonstrate the pharmacokinetics equivalence of CT-P10 and reference rituximab (MabThera) in patients with rheumatoid arthritis. Efficacy outcomes including ACR and EULAR response rates, time to onset of ACR20 response and mean changes from baseline in DAS28 score, CDAI and SDAI were secondary endpoints of the trial. Patients enrolled in Study CT-P10 1.1 could receive 1or 2 courses of rituximab, and were eligible for inclusion in the subsequent, open label, maintenance trial (Study CT-P10 1.3) where they could receive 1 additional course of CT-P10 (including those subjects who previously received MabThera in Study CT-P10 1.1). Study CT-P10 1.3 was primarily designed to assess the medium term efficacy and safety of CT-P10 in a small subgroup of patients with rheumatoid arthritis. In general, the supporting rheumatoid arthritis studies had complicated but fitting designs (particularly, Study CT-P10 1.1), assessed the appropriate efficacy endpoints and had suitable pre-specified statistical analysis plans for the efficacy outcomes, which were mainly reported using descriptive statistics for the efficacy (Study CT-P10 1.1) and intention-to-treat populations (Study CT-P10 1.3).

The patient populations enrolled in Studies CT-P10 1.1 and Study CT-P10 1.3 consisted of adult patients with long standing rheumatoid arthritis (around 10 years duration) that was moderately to severely active at baseline. In addition, subjects had a history of inadequate response or intolerance to DMARDs including one or two anti-TNF drugs and weekly low dose methotrexate (10 to 25 mg). The eligibility criteria were generally consistent with the approved rheumatoid arthritis treatment indication for rituximab in

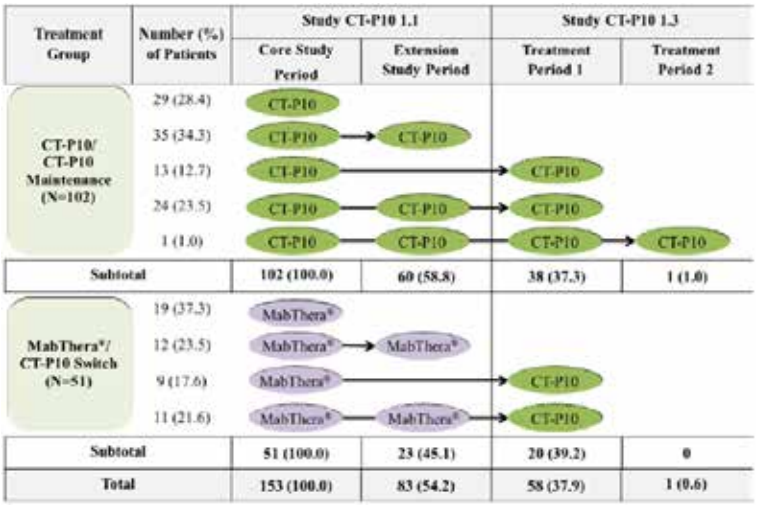
[13] CPMP/EWP/556/95 Rev 1 Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis

Australia, although currently it is limited to severely active disease only. The sponsor justifies the widening of the eligibility criteria in the CT-P10 studies to include those with moderately active disease baseline based on the published historical data for rituximab in rheumatoid arthritis, which therefore allows the CT-P10 rheumatoid arthritis dataset to be compared with historical results. This is an acceptable justification for the CT-P10 study program in patients with rheumatoid arthritis.

In Study CT-P10 1.1, the mean scores for disease activity as measured by DAS28 decreased from baseline up to and including Week 24 in both treatment groups (CT-P10 and MabThera), were similar between the two arms, and within historical expectations for rituximab. Post hoc analysis of the data recorded in Study CT-P10 1.1 supported the claim of therapeutic equivalence between CT-P10 and MabThera with the 95% CIs for the mean change from baseline to Week 24 in DAS28-CRP scores being completely within the CHMP recommended equivalence margin of ± 0.6. In addition, the rates of categorical ACR and EULAR response at Weeks 8, 16 and 24 were similar between the two treatment groups at each time point, although generally higher for both arms at Weeks 16 and 24 versus Week 8, which is consistent with historical expectations.

Study CT-P10 1.3 was an open label, single arm, treatment maintenance trial with the main objective of demonstrating the long term efficacy and safety of CT-P10 in patients with rheumatoid arthritis who were treated with either MabThera or CT-P10 in Study CT-P10 1.1. After the last study visit in the core study period of Study CT-P10 1.1 (Week 48) or the last visit in the extension study phase of Study CT-P10 1.1 (that is, Week 24 of the extension period, or up to Week 72 of the entire study period), eligible subjects had the opportunity to receive CT-P10 (that is, either continued therapy with CT-P10 or a switch from MabThera to CT-P10) for a maximum of 56 weeks in the maintenance study phase of Study CT-P10 1.3. The total duration of subject involvement (main + maintenance study period) was up to 104 weeks. Figure 2 summarises the number of subjects by quantity of rituximab treatment courses throughout Studies CT-P10 1.1 and CT-P10 1.3.

Figure 2: Subjects by number of treatment courses throughout Studies CT-P10 1.1 and Study CT-P10 1.3



As of the data cut-off, only 1 subject (continuously treated with CT-P10) has received four courses of rituximab. All other subjects had received either 2 or 3 rituximab treatment courses across the two trials. Efficacy data following repeat (either 2 or 3) treatment courses of rituximab (with up to 104 weeks of treatment follow-up in total) in Studies CT-P10 1.1 and 1.3 indicated that the rate of ACR20 and DAS28/EULAR responses were maintained in those who continued to receive CT-P10 (n = 38 subjects) and were

similar in those subjects who switched from MabThera to CT-P10 (n = 20 subjects) in the open label, maintenance trial.

In conclusion, efficacy data from the primary pharmacokinetics equivalence trial in rheumatoid arthritis patients (Study CT-P10 1.1) and its open label maintenance phase (Study CT-P10 1.3) provides moderately robust clinical efficacy outcomes to support the claim of therapeutic equivalence of CT-P10 with MabThera for the treatment of active rheumatoid arthritis after failure or intolerance of anti-TNF therapy.

Pivotal efficacy study for lymphoma treatment indication

Study CT-P10 3.3

Study design, objectives, locations and dates

Study CT-P10 3.3 was a Phase I/III, two part, randomised, parallel group, active controlled, double blind trial with two primary endpoints designed to demonstrate similarity in pharmacokinetics (Part 1), as well as non-inferiority in efficacy (Part 2) of CT-P10 to Rituxan, when each rituximab therapy is co-administered with cyclophosphamide, vincristine and prednisone (CVP) in adult patients with advanced follicular lymphoma. The primary objective of Part 1 of the study was to demonstrate similar pharmacokinetics between CT-P10 and Rituxan at steady state (that is, at core Cycle 4). The primary objective of Part 2 of Study CT-P10 3.3 was to demonstrate that CT-P10 was non-inferior to Rituxan in terms of efficacy as determined by the overall response rate (ORR). The overall response rate was defined as the proportion of responder patients who achieved complete response (CR) plus unconfirmed complete response (CRu) plus partial response (PR) over 8 cycles of treatment in the core study period of Study CT-P10 3.3. The Overall Response Rate definition used in Study CT-P10 3.3 was consistent with the 1999 International Working Group (IWG) criteria in previously untreated patients with advanced (stage III or IV) CD20+ follicular lymphoma.

Evaluator commentary

The primary objective of Part 2 of Study CT-P10 3.3 was to evaluate the clinical efficacy of CT- P10 in comparison to Rituxan using overall response rate (the proportion of responders who achieved complete response, unconfirmed complete response or partial response as per the 1999 IWG criteria) over 8 cycles of treatment in the core study period. From central review using the per protocol cohort, the overall response rate was 97.0% (64 of 66) in the CT-P10 treatment group and 92.6% (63 of 68) in the Rituxan arm. The overall response rate during the core study period according to the 1999 IWG criteria for the intention to treat population was 95.0% (67 of 70) in the CT-P10 group and 90.0% (63 of 70) in the Rituxan arm. The treatment related difference in the overall response rate between CT-P10 and Rituxan (using central review) was 4.3% in the per protocol population and 5.7% in the intention to treat population, both of which lie on the positive side of the non-inferiority margin using a point estimate difference of 7% based on reference product (rituximab-MabThera) variability, as defined in the trial protocol and justified by the relevant literature. Supporting analyses of the primary efficacy outcome supported the main statistical analysis observation. In particular, the overall response rate results based on local review were consistent with those of central review in both the per protocol and intention to treat populations. Moreover, the overall response rate in the anti-drug antibodies negative subset of both the per protocol and intention to treat populations showed a similar trend with the primary analyses.

In addition, the proportion of patients with clearance of bone marrow involvement with lymphoma and resolution of B-symptoms at 24 weeks was similar between the CT-P10 and Rituxan treatment groups. The limited number of secondary efficacy outcomes reported thus far support the scientific robustness of the primary efficacy endpoint in Part 2 of Study CT-P10 3.3.

Other efficacy studies for lymphoma treatment indication

Study CT-P10 1.2

Study CT-P10 1.2 was a Phase I, open label, single-arm trial primarily designed to evaluate the safety of CT-P10 (IV 375 mg/m^2 on day 1 of each cycle) in combination with dexamethasone, cytosine arabinoside and cisplatin (DHAP) in approximately 10 adult Asian patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Study CT-P10 3.4

The submission contained a protocol synopsis for Study CT-P10 3.4. No patient specific data was included in the dossier as the trial is still recruiting subjects. Study CT-P10 3.4 is a Phase III, randomised, parallel group, active controlled, double blind trial designed to evaluate the comparative efficacy and safety of CT-P10 and Rituxan in subjects with low tumour burden follicular lymphoma (grade 1 to 3a; Ann Arbor stage II, III or IV disease). It is expected that approximately 125 study centres in Europe, Africa, Middle East, Asia Pacific and Latin and North America will be participating in this trial

Evaluator commentary: other efficacy studies for lymphoma indication

With only 1 subject enrolled in Study CT-P10 1.2, meaningful efficacy conclusions cannot be drawn. However, the patient did achieve partial response after 2 cycles of treatment and was eligible for autologous stem cell transplant (ASCT), for a condition (DLBCL) that carries a poor prognosis.

Study CT-P10 3.4 is an appropriately designed and statistically powered trial to evaluate the stated objectives. When the trial results are available (expected in 2021) they will be supportive and informative about the biosimilarity of CT-P10 and the appropriate reference rituximab product.

Justification for extrapolation of treatment indications

In the submission, the sponsor provided a literature review of the evidence supporting extrapolation of treatment indications based on the clinical data with CT-P10 in the rheumatoid arthritis (autoimmune indication) and advanced follicular lymphoma populations (oncology treatment indication). The guideline;[11] notes that:

> '*extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibody (mAb), not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. Applicants should support such extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action*.'

The extrapolated adult treatment indications requested for CT-P10 include ANCA associated systemic vasculitis (second autoimmune disease indication) and CLL (which is a closely related oncology indication to NHL).

The sponsor has provided a detailed explanation justifying the extrapolation of rituximab data to all of the proposed treatment indications on the basis of the comparable mechanisms of action, pharmacokinetics and efficacy of the examined rituximab formulations. Overall, the sponsor has justified the extrapolation to the two non-examined treatment indications by using rheumatoid arthritis as the autoimmune model (most internally homogeneous treatment population) and advanced follicular lymphoma as the oncology model. Published evidence indicates that the presence of CD20 antigen on the surface of B-cells in autoimmune and lymphoproliferative disorders unifies responsiveness to rituximab, which in thereafter drives the overlapping CD20-dependent mechanisms of B-cell depletion that results in either reduction of tumour burden or amelioration of the autoimmune disease.

One particular issue raised in the application was the extrapolation of treatment indication to include ANCA associated vasculitis, specifically because of concomitant glucocorticoid use on a daily basis over a 6 month period following induction of remission with rituximab. In the other three approved treatment indications, glucocorticoid therapy is used either intermittently (with each rituximab infusion administration) or in low daily dose (for example, prednisone < 7.5 mg daily in a subset of patients with difficult to control rheumatoid arthritis). Based on population pharmacokinetics data obtained in the pivotal MabThera registration study in ANCA associated vasculitis (the RAVE study[14]), the pharmacokinetics parameters of rituximab in GPA and MPA patients are similar to that observed in rheumatoid arthritis patients, and the incidence of positive anti-drug antibodies testing is also similar in the two autoimmune treatment populations. Furthermore, a comprehensive review of the literature did not yield any evidence to suggest that B-cell depletion in autoimmune and oncology disorders occurs differently despite the conditions having distinct pathophysiology and clinical manifestations.

Analyses performed across trials: pooled and meta-analyses

No pooled or meta-analyses were provided in the submission. Efficacy data from Studies CT-P10 1.1 and CT-P10 3.2 were compared to historical data reported in the pivotal Phase III rheumatoid arthritis registration study (REFLEX study[15]) and the supportive Phase IIb registration study (the DANCER study [16]), both of which had a similar design and eligibility criteria to those applied across Studies CT-P10 1.1 and CT-P10 3.2. The REFLEX study had a randomised design and used the same rituximab dosage regimen as the CT-P10 trials. Further courses of MabThera (2 x 1000 mg + methotrexate) were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of MabThera. The comparison between the efficacy data observed in Studies CT-P10 1.1 and CT-P10 3.2 versus the historical data for MabThera revealed very similar clinical responses in patients with active rheumatoid arthritis in terms of the frequency and magnitude of benefit with CT-P10 and comparator rituximab therapies.

Evaluator's conclusions on efficacy

Rheumatoid arthritis

The clinical development program for CT-P10 in patients with rheumatoid arthritis includes a Phase I pharmacokinetics equivalence study between CT-P10 and the EU reference product MabThera (Study CT-P10 1.1), followed by a therapeutic equivalence Phase III trial (Study CT-P10 3.2). The Phase III study had two parts; Part 1 was designed to evaluate the 3-way pharmacokinetics equivalence of CT-P10 against reference rituximab formulations (MabThera and Rituxan), and Part 2 was aimed at establishing therapeutic equivalence between CT-P10 and the combined reference rituximab cohort (MabThera + Rituxan).

The Phase I pharmacokinetics equivalence Study CT-P10 1.1 in rheumatoid arthritis patients had an extension phase to assess the long-term safety and efficacy of repeat treatment up to Week 104 (Study CT-P10 1.3). In the pivotal rheumatoid arthritis trial (Study CT-P10 3.2), efficacy results in terms of DAS28 and ACR response were shown to be

[14] Stone JH, et al. Rituximab versus cyclophosphamide for ANCA associated vasculitis. *N Engl J Med* 2010; 363: 221-222

[15] Cohen SB et al (REFLEX Trial Group). Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomised, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54: 2793-2806

[16] Emery P, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomised, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006; 54: 1390-1400

comparable between CT-P10 and MabThera over 48 weeks of treatment follow-up. In addition, the Phase I trial (Study CT-P10 1.1) and its open label maintenance phase (Study CT-P10 1.3) support the efficacy of repeat treatment up to 104 weeks with CT-P10 (up to 3 courses in 36 subjects in total; only 1 subject thus far has received 4 treatment courses in total). Overall, the biosimilarity of CT-P10 and MabThera in adult patients with active rheumatoid arthritis has been demonstrated based on the efficacy data provided in this submission.

Lymphoma

Study CT-P10 3.3 was a supportive study to confirm the biosimilarity of CT-P10 in the oncology treatment setting. The main 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 co-administered with CVP in patients with advanced follicular lymphoma. Focusing on the efficacy results of Part 2, only overall response rate according to 1999 IWG criteria has been submitted. Overall response rate as per the 2007 IWG criteria and various time-to-event parameters including progression free survival, response duration and overall survival will be included in the final report of the study.

Overall response rate is an acceptable endpoint for this application of biosimilarity in the follicular lymphoma indication. The sponsor established an equivalence margin of 7%, even though and according to the sponsor the non-inferiority margin was based on absolute point estimate difference and not by using 95% CI approaches. The 7% is based on an expected overall response rate of 81% in the literature. Overall, the calculation of the non-inferiority margin is acceptable from a clinical perspective and consistent with the EMA guideline on the choice of non-inferiority margin. On analysing the overall response rate (central review) both in per protocol and intention to treat populations, the treatment related difference lies within 7% (4.3% and 5.7% per protocol and intention to treat respectively). Overall response rate appears slightly superior to CT-P10 and the pattern of the responses points towards more complete response and similar partial response, but the number of cases of unconfirmed complete response could change these values. The lower bound for 95% CI in both the per protocol and intention to treat populations would lie within 7%. The objectives of Study CT-P10 3.3 (up to Week 24) were met and extrapolation in the context of treating patients with NHL and CLL with CT-P10 is acceptable.

Extrapolation of treatment indications (CLL and ANCA associated vasculitis)

Regarding the extrapolation of treatment indications from the studied cohorts, the sponsor has provided substantial evidence from non-clinical studies (not assessed as part of this report) that show similarity in structure for CT-P10 compared to reference rituximab formulations. In conjunction with the bioequivalence data from the pharmacokinetics studies, the efficacy data observed in patients with rheumatoid arthritis (Studies CT-P10 3.2, 1.1 and CT-P10 1.3) and those with lymphoma (Study CT-P10 3.3) provides evidence to suggest similar responses for CT-P10 and MabThera in medical conditions that share common mechanisms of pathology to rheumatoid arthritis (ANCA vasculitis) and advanced follicular lymphoma (NHL and CLL).

Extrapolation of the pharmacokinetics and efficacy data to other approved autoimmune and oncology treatment indications is justifiable on the basis of the results of the extensive pre-clinical studies supported by the evidence that rheumatoid arthritis and lymphoma share similar and overlapping pathophysiological immunological mechanisms and response to rituximab. The extent and type of data submitted to justify approval of CT-P10 is in keeping with the TGA adopted EMA guideline.[11] Therefore, there is sufficient evidence to approve CT-P10 for all adult treatment indications for which MabThera is currently approved in Australia. This recommendation is consistent with the prior decisions of the

TGA (and the EMA) with respect to extrapolation of treatment indications for other complex biosimilar therapies such as anti-TNF medicines.

Safety

Studies providing safety data

In this submission, there were two ongoing, pivotal efficacy/safety trials (Study CT-P10 3.2 in patients with rheumatoid arthritis and Study CT-P10 3.3 in subjects with advanced follicular lymphoma), which collected the following safety data:

- Adverse events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed at Weeks 2, 8, 24 and 26, every 8 to 12 weeks thereafter in Study CT-P10 3.2; and Day 1 of every treatment cycle in Study CT-P10 3.3.
- AEs of particular interest, including serious infection, tuberculosis and infusion related reactions (IRRs) were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology (central lab), clinical chemistry (central lab) and urinalysis (central lab), were performed at baseline, Weeks 2, 8, 24 and 26, and every 8 weeks thereafter in Study CT-P10 3.2; and Day 1 of every treatment cycle in Study CT-P10 3.3.
- Screening tests for tuberculosis (chest x-ray and QuantiFERON Gold testing) were routinely taken at baseline, and were performed again if tuberculosis was suspected thereafter.
- Vital signs such as blood pressure, heart rate and temperature were performed at each scheduled study visit. Complete physical examination was performed at screening (including subject weight) and was abbreviated at subsequent visits (discretion of the site investigator).
- 12-lead ECG for central reading was taken at baseline and with each infusion episode in both trials and as required by clinical indication up to Week 48.
- Urine pregnancy testing was performed at baseline and prior to every infusion episode in females.
- Serum for Anti-Drug Antibodies (anti-drug antibodies) to rituximab was collected at baseline, as well as Weeks 24 and 48 (or end of study visit) in Study CT-P01 3.2. In Study CT-P10 3.3, blood samples for immunogenicity testing were collected at baseline, after the fourth Cycle and at the end of treatment visit. Analysis occurred via central laboratory.
- Serum for immunoglobulin (IgM, IgG and IgA) levels was collected at specified time points in both pivotal studies. Analysis occurred via central laboratory.

The MedDRA system (version 18.1 or higher) was used to code all treatment emergent Adverse Events (AEs). Listings for AEs were provided by treatment group and trial, and categorised by System Organ Class (SOC) and Preferred Term (PT).

Other studies

Studies CT-P10 1.1 and CT-P10 1.3

Study CT-P10 1.1 was a Phase I, double blind trial that enrolled a total of 154 adult subjects with rheumatoid arthritis. Blood for haematology, clinical chemistry and viral

serology, as well as vital signs, tuberculosis evaluation and a 12- lead ECG were performed at baseline. The assessment for AEs (including infusion related reactions) was conducted at every infusion episode and every 8 weeks during the 48 week core and extension study periods. Clinical laboratory tests (haematology and clinical chemistry) were repeated prior to each infusion episode and every 8 weeks. Serum for anti-drug antibodies testing was also collected at baseline and every 8 weeks throughout the trial.

Study CT-P10 1.3 was a single-arm, open label, safety maintenance trial of the Phase I Study CT-P10 1.1. Safety assessments were performed at each CT-P10 infusion episode and every 8 weeks up to Week 24 (or the end of study visit) in Study CT-P10 1.3.

Study CT-P10 1.2

Only 1 subject (30 year old female) with relapsed CD20+ DLBCL was enrolled and completed treatment up to Cycle 3 in this Phase I, open label trial. A total of 20 AEs were reported in this patient and 6 of those were judged to be related to CT-P10. The treatment related AEs were 4 episodes of neutropenia (3 of grade 4 intensity and 1 of grade 3 severity), thrombocytopenia (grade 3) and constipation (grade 2). All of these AEs resolved spontaneously or with treatment. No serious AEs (SAEs) were reported. During the study period, no other clinically significant laboratory abnormalities (apart from neutropenia) were observed. Vital signs and ECG readings remained within normal limits. The immunogenicity results were all negative (screening, Cycle 3 and the end of study visit).

Patient exposure

The studies reported in the submission provide an overall safety database of 666 rheumatoid arthritis patients who were treated with at least 1 dose (full or partial) of CT-P10, MabThera or Rituxan during any dosing period. Of these, 354 subjects have been exposed to CT-P10 and 322 patients have received reference rituximab. Moreover, there is a small amount of information in 20 subjects who switched from MabThera to CT-P10 (single 1-way rituximab treatment switch) in Study CT-P10 1.3. For the rheumatoid arthritis population, the safety dataset comprises a total of 525 patients which includes 35 subjects who have been followed for up to 2 years (104 weeks) in Studies CT-P10 1.1 and 1.3, as well, 372 patients in Study CT-P10 3.2 who have been followed for up to 48 weeks. Additional safety information in an oncology indication was also available in this submission. A total of 140 patients treated with rituximab (70 in each treatment group) for advanced follicular lymphoma and exposed for up to 6 months (24 weeks) in Study CT-P10 3.3 were presented.

In Study CT-P10 3.2, patients with rheumatoid arthritis received up to 4 infusions of study drug via 2 treatment courses (up to Week 48 of the main study period) in combination with methotrexate and folic acid. Each treatment course consisted of 2 infusions of study drug (1000 mg of CT-P10, MabThera or Rituxan by IV infusion) with a 2-week interval between the first and second infusions. The mean (SD) total number of doses of rituximab were similar between the treatment groups being 3.7 (0.79) doses in CT-P10 group, 3.9 (0.48) doses in MabThera arm and 3.8 (0.67) doses in the Rituxan arm. Furthermore, the proportions of patients who received the full rituximab dose of 4000 mg in Study CT-P10 3.2 were similar among the three treatment groups: 87.6% (141 of 161) of patients in the CT-P10 group, 95.0% (57 of 60) of subjects in the MabThera arm and 90.7% (137 of 151) of patients in the Rituxan group. Table 4 provides a summary of the total exposure to study rituximab up to Week 48 in Study CT-P10 3.2 (Part 2 safety population).

Table 4: Exposure to CT-P10, MabThera or Rituxan up to Week 48 in Study CT-P10 3.3 (Part 2)

	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 (100.0)	60 (100.0)	151 (100.0)	211 (100.0)	372 (100.0)
Main Week 2	154 (95.7)	59 (98.3)	147 (97.4)	206 (97.6)	360 (96.8)
Main Week 24	142 (88.2)	58 (96.7)	138 (91.4)	196 (92.9)	338 (90.9)
Main Week 26	141 (87.6)	57 (95.0)	137 (90.7)	194 (91.9)	335 (90.1)

Note: During the 1st treatment course, there were 12 patients who did not receive full dose of 2,000 mg; 6 patients received partial dose of the 1st infusion and 6 patients did not receive the 2nd infusion after receiving the full dose of the 1st infusion. Among patients who initiated the 2nd treatment course, 3 patients did not received the full dose of 2,000 mg; 3 patient did not received the 2nd infusion after receiving full dose of the 1st infusion.

In Study CT-P10 1.1, patients with rheumatoid arthritis received up to two courses of rituximab in combination with methotrexate. The mean (SD) total number of rituximab doses received in Study CT-P10 1.1 was 3.2 (1.00) doses in the CT-P10 group and 2.8 (1.01) doses in the MabThera arm. Both groups recorded a mean of 2.0 rituximab doses in the core study period, as well as the extension phase (2.0 and 1.9 doses for the CT-P10 and MabThera groups, respectively). Of those patients who received rituximab in Study CT-P10 1.3 (maintenance study period), 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 CT-P10 switch groups.

In Study CT-P10 3.3, the majority of patients in each treatment group received the study rituximab (CT-P10 or Rituxan) for all cycles up to core Cycle 8 as summarised in Table 5.

Table 5: Exposure to CT-P10 or Rituxan up to Core Cycle 8 in Study CT-P10 3.3

	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (N=70)	Total (N=140)
	Overall Exposure - Number (%) of Patients		
Core Cycle 1 at Week 0	70 (100.0)	70 (100.0)	140 (100.0)
Core Cycle 2 at Week 3	69 (98.6)	68 (97.1)	137 (97.9)
Core Cycle 3 at Week 6	68 (97.1)	66 (94.3)	134 (95.7)
Core Cycle 4 at Week 9	66 (94.3)	66 (94.3)	132 (94.3)
Core Cycle 5 at Week 12	64 (91.4)	65 (92.9)	129 (92.1)
Core Cycle 6 at Week 15	63 (90.0)	64 (91.4)	127 (90.7)
Core Cycle 7 at Week 18	62 (88.6)	63 (90.0)	125 (89.3)
Core Cycle 8 at Week 21	62 (88.6)	62 (88.6)	124 (88.6)

Safety issues with the potential for major regulatory impact

Deaths and serious adverse events (SAEs)

In the pooled analysis for the rheumatoid arthritis population, the type and incidence of treatment emergent SAEs was similar between the total CT-P10 group (CT-P10 only plus those who switched to CT-P10) and the reference products arm (MabThera + Rituxan) groups: 29 patients (10.2% of 283) in the total CT-P10 group (including 28 subjects reporting 33 SAEs in the CT-P10 alone cohort and 1 subject reporting 1 SAE in the switch subgroup), and 23 subjects (8.8% of 262) reporting 25 SAEs in the reference products group. In general, there were no significant differences between CT-P10 and reference rituximab treated subjects for the incidence and type of SAEs apart from 2 thrombo-embolic SAEs in CT-P10 subjects versus no such cases in the comparator cohort, and 4

cases (1.5%) of neoplasm in the reference rituximab group versus only 1 SAE in the total CT-P10 arm (0.4%). Each treatment cohort (total CT-P10 versus reference rituximab) recorded 3-4 infection related SAEs.

Study CT-P10 3.2

One subject died during Study CT-P10 3.2. A 58 year old female developed the SAE of suspected right brachial vein thrombosis and cellulitis approximately 7 weeks after receiving her initial course of CT-P10. She was hospitalised for the SAE and had a positive culture for Staphylococcus aureus from the right arm skin swab. With antibiotic treatment, the patient felt better but complained of diarrhoea and this led to discontinuation of antibiotics after 10 days. The patient also subsequently had an echocardiogram that didn't identify any upper limb vascular thrombosis, but raised the suspicion of cellulitis after discontinuation of antibiotics. Therefore, antibiotic treatment was resumed. However, her clinical condition worsened and she died due to acute respiratory distress about 3 weeks after the SAE was first recognised (that is, 72 days after the last infusion of CT-P10). The site investigator believed that the patient suffered cellulitis with secretion from the skin leading to hypoalbuminemia and an inability to maintain osmotic pressure, which in turn led to respiratory deterioration. The death was considered by the site investigator to be unrelated to study drug. However, upon the sponsor's review of the case, the presence of pulmonary embolism had not been fully excluded in the absence of spiral CT chest scan and serious infections are a recognised risk factor with rituximab.

In Study CT-P10 3.2, a total of 29 patients reported at least 1 treatment emergent SAE including 13 patients (8.1% of 161) reporting 15 SAEs in the CT-P10 group, 2 subjects (3.3% of 60) recording 2 SAEs in the MabThera group and 14 patients (9.3% of 151) reporting 15 SAEs in the Rituxan group. All of the SAEs reported in the CT-P10 group were considered to be unrelated to the study drug. One MabThera treated subject (1.7% of 60) and 5 patients (3.3% of 151) in the Rituxan group were considered to have treatment related SAEs.

The most frequently reported SAE in the CT-P10 group was fracture, which was reported in 4 subjects (2.5%). In the Rituxan arm, fracture and injury was reported for 2 (1.3%) patients. No other type of SAE was reported for more than 1 patient in any of the three treatment groups. However, a total of 5 infectious SAEs were observed in Study CT-P10 3.2 including 2 cases of cellulitis (1 each in the CT-P10 and Rituxan groups), 2 cases of pneumonia (1 each in the CT-P10 and Rituxan groups) and 1 lower respiratory tract infection (Rituxan treated subject). There were 3 serious haematological disorders with 1 case of agranulocytosis in a CT-P10 treated subject, 1 report of leucopenia in a MabThera treated patient and 1 case of pancytopenia in a Rituxan treated subject. In addition, 3 cases of malignancy were recorded with colonic adenocarcinoma in a MabThera treated subject, and 1 case each of breast and bladder cancer in Rituxan treated subjects. Other noteworthy SAEs reported in the CT-P10 group were single cases of acute kidney injury, myocardial ischaemia and vena cava thrombosis.

Study CT-P10 3.3

One patient died during the course of Study CT-P10 3.3, and another 2 deaths were reported after treatment discontinuation. A 74 year old female patient who was treated with 1 Cycle of CT-P10 in combination with CVP experienced tumour lysis syndrome 12 days later and died due to cardiac and renal failure 16 days after receiving treatment. This death was judged by the investigator to have a possible relationship with study medication and tumour lysis syndrome is an identified risk with MabThera (documented in the PI for lymphoma patients). The subject had a known history of coronary artery disease and hypertension with impaired renal function at baseline. Poor hydration during hospitalisation was a compounding factor and no allopurinol was given prior to initiating the rituximab+CVP regimen.

The 2 deaths that were reported following premature discontinuation were due to disease progression and the associated deterioration in health status. One subject (41 year old female) withdrew from the study because of disease progression after 2 cycles of treatment and the other patient (61 year old female) ceased trial involvement because of recurrent infusion related reaction (received 4 study treatment cycles in total).

In Study CT-P10 3.3, a total of 25 patients reported at least 1 treatment emergent SAE including 16 patients (22.9% of 70) reporting 29 SAEs in the CT-P10 group and 9 subjects (12.9% of 70) recording 11 SAEs in the Rituxan arm. A minority of SAEs were considered to be related to study treatment: 6 patients (8.6% of 70) in the CT-P10 group and 4 subjects (5.7% of 70) in the Rituxan arm. Overall, the most frequently reported type of SAE was febrile neutropenia, which was reported for 2 (2.9%) patients in each treatment group. Table 6provides a summary of SAEs reported in Study CT-P10 3.3. Although the number of events is small there are some notable differences in the incidence of SAEs between the CT-P10 and Rituxan groups. In particular, there were 5 serious infections (7.1%) in the CT-P10 group versus 2 (2.9%) in the Rituxan arm plus 2 SAEs of thromboembolic disease (DVT or PE) in the CT-P10 group versus no such SAEs in the comparator arm.

Table 6: Summary of serious adverse events in Study CT-P10 3.3 (Safety Population)

System Organ Class Preferred Term	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (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	**4 (5.7)**	**3 (4.3)**	**7 (5.0)**
Anaemia (unrelated, grade 2)	1 (1.4)	0	1 (0.7)
Febrile neutropenia (related, grade 3)	0	1 (1.4)	1 (0.7)
Febrile neutropenia (unrelated, grade 3)	2 (2.9)	1 (1.4)	3 (2.1)
Leukopenia (related, grade 3)	0	1 (1.4)	1 (0.7)
Neutropenia (related, grade 4)	1 (1.4)	0	1 (0.7)
Neutropenia (unrelated, grade 4)	1 (1.4)	0	1 (0.7)
Pancytopenia (related, grade 3)	1 (1.4)	0	1 (0.7)
Cardiac disorders	**1 (1.4)**	**0**	**1 (0.7)**
Angina pectoris (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Atrial fibrillation (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Gastrointestinal disorders	**2 (2.9)**	**2 (2.9)**	**4 (2.9)**
Constipation (unrelated, grade 2)	1 (1.4)	0	1 (0.7)
Diarrhoea (unrelated, grade 3)	0	1 (1.4)	1 (0.7)
Ileus (related, grade 4)	0	1 (1.4)	1 (0.7)
Small intestinal perforation (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
General disorders and administration site conditions	**0**	**1 (1.4)**	**1 (0.7)**
Pyrexia (unrelated, grade 2)	0	1 (1.4)	1 (0.7)
Hepatobiliary disorders	**1 (1.4)**	**0**	**1 (0.7)**
Cholecystitis (unrelated, grade 2)	1 (1.4)	0	1 (0.7)
Immune system disorders	**1 (1.4)**	**0**	**1 (0.7)**
Anaphylactic shock (related, grade 3)	1 (1.4)	0	1 (0.7)
Infections and infestations	**5 (7.1)**	**2 (2.9)**	**7 (5.0)**

Table 6 (continued): Summary of serious adverse events in Study CT-P10 3.3 (Safety Population)

System Organ Class Preferred Term	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (N=70)	Total (N=140)
	Number (%) of Patients		
Abdominal infection (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Campylobacter gastroenteritis (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Encephalitis (related, grade 3)	0	1 (1.4)	1 (0.7)
Lower respiratory tract infection (unrelated, grade 2)	0	1 (1.4)	1 (0.7)
Lower respiratory tract infection (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Pneumonia (related, grade 3)	1 (1.4)	0	1 (0.7)
Pneumonia (unrelated, grade 3)	2 (2.9)	0	2 (1.4)
Injury, poisoning and procedural complications	**1 (1.4)**	**1 (1.4)**	**2 (1.4)**
Post procedural fistula(unrelated, grade 2)	1 (1.4)	0	1 (0.7)
Subdural haematoma (unrelated, grade 3)	0	1 (1.4)	1 (0.7)
Investigations	**1 (1.4)**	**0**	**1 (0.7)**
Liver function test abnormal (related, grade 3)	1 (1.4)	0	1 (0.7)
Metabolism and nutrition disorders	**2 (2.9)**	**0**	**2 (1.4)**
Hypoalbuminaemia (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Hypocalcaemia (unrelated, grade 4)	1 (1.4)	0	1 (0.7)
Hypomagnesaemia (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Tumour lysis syndrome (related, grade 5)	1 (1.4)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**3 (4.3)**	**1 (1.4)**	**4 (2.9)**
Chronic obstructive pulmonary disease (unrelated, grade 3)	2 (2.9)	1 (1.4)	3 (2.1)
Pleural effusion (unrelated, grade 2)	1 (1.4)	0	1 (0.7)
Pulmonary embolism (unrelated, grade 3)	1 (1.4)	0	1 (0.7)
Vascular disorders	**1 (1.4)**	**1 (1.4)**	**2 (1.4)**
Deep vein thrombosis (related, grade 2)	1 (1.4)	0	1 (0.7)
Thrombophlebitis (unrelated, grade 2)	0	1 (1.4)	1 (0.7)

Other rheumatoid arthritis studies

No deaths were reported in Studies CT-P10 1.1 and CT-P10 1.3.

In Study CT-P10 1.1 (with unequal randomisation of 2:1), a total of 21 patients reported at least 1 treatment emergent SAE including 14 patients (13.7% of 102) reporting 17 SAEs in the CT-P10 group and 7 subjects (13.7% of 51) recording 8 SAEs in the MabThera arm. A small proportion of subjects had SAEs were considered to be related to study treatment: 2.9% (3 of 102) in the CT-P10 group and 3.9% (2 of 51) in the MabThera arm. The only type of SAE recorded in 2 or more subjects was intervertebral disc disorder (2 patients in the MabThera group; considered unrelated). The single SAE cases of note in the CT-P10 group were uveitis, diverticulitis, osteonecrosis, adrenal neoplasm, cerebral infarction, rash and deep vein thrombosis (all of which were deemed to be unrelated except osteonecrosis). The single SAE cases of note in the MabThera group were neutropenia (considered to be treatment related), pneumonia (drug related) and early stage cervical carcinoma (judged as unrelated).

In Study CT-P10 1.3, among patients who received rituximab in the maintenance study period, 1 patient in each treatment group recorded the SAE of spinal osteoarthritis, both which were deemed unrelated to study treatment.

Discontinuations due to adverse events

Integrated rheumatoid arthritis safety analysis

The pooled analysis data for the rheumatoid arthritis population showed 3.2% (9 of 283) of patients in the total CT-P10 group and 5.0% (13 of 262) of subjects in the reference rituximab cohort experienced at least 1 AE leading to permanent treatment discontinuation. In both treatment cohorts, the most frequently reported AE leading to cessation was an infusion related reaction, which was reported for 4 patients in each treatment group.

Liver function and liver toxicity

Across the rheumatoid arthritis studies, the most frequently reported abnormality of liver function tests was increased gamma glutamyl transferase (GGT). In Study CT-P10 3.2, raised GGT was recorded for a total of 9 patients (2 (1.2%) in the CT-P10 group and 7 (3.3%) in the reference rituximab arm). In Study CT-P10 1.1, 6 (5.9% of 102) patients in the CT-P10 group and 1 (2.0% of 51) in the MabThera arm were observed to have grade 3 increases in serum GGT. In Study CT-P10 3.3, 3 CT-P10 treated subjects (4.3% of 70) recorded grade 3 increases in GGT versus no such cases in the Rituxan arm. No other significant abnormalities of liver function tests were observed in the CT-P10 clinical study program (for either rheumatoid arthritis or advanced follicular lymphoma).

Cases of hepatitis B virus (HBV) reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcIg) should consult liver disease experts before starting rituximab and should be monitored and managed according to local standards to prevent HBV reactivation. In line with the MabThera PI, patients were assessed for HBsAg, HBsAb and HBcIg before exposure to study drug in all of the CT-P10 clinical studies. For patients who were enrolled based on the DNA test, the DNA test was repeated every 24 weeks (± 8 weeks) for monitoring purposes. In addition, HBsAg, HBsAb, HBcIg and DNA tests were performed for the patients having suspected hepatic symptoms during the study periods of the CT-P10 rheumatoid arthritis and NHL studies. Across all of the CT-P10 studies there were no reported cases of fulminant hepatitis. However, some patients had positive HBV DNA test results identified in the trials.

In Study CT-P10 3.2, 2 patients in the CT-P10 group recorded positive results for the HBV DNA test (one at Week 24, the other identified at the Week 48 visit). At screening visit, both patients had negative results for HBsAb and HBsAg, and a positive result for HBcIg, and were enrolled based on the negative result for HBV DNA. The results of the liver function tests for both patients were within the normal range with no clinical sequelae reported for these patients.

In Studies CT-P10 1.1 and CT-P10 1.3, 1 patient in the CT-P10 maintenance treatment group tested positive for HBV DNA. This patient had a positive result for HBsAb and HBcIg at screening and was enrolled based on a negative result for the HBV DNA test. Thus, the hepatitis B monitoring via HBV DNA test was performed for this patient in accordance with the study protocol. The patient entered into the maintenance study (CT-P10 1.3), but was not treated with any additional CT-P10 during Study CT-P10 1.3. All liver function tests for this subject were within the normal range except for a borderline high ALT (34 U/L) at Week 2 in Study CT-P10 1.1. In Study CT-P10 3.3, no patient recorded hepatitis B reactivation or positive HBV DNA results.

Renal function and renal toxicity

No subjects in the rheumatoid arthritis trials developed clinically significant abnormalities in renal function apart from 1 CT-P10 treated subject in Study CT-P10 3.2. This subject experienced a grade 3 increase in serum creatinine that was considered to be unrelated to

treatment. No significant changes in renal function or toxicity were observed in Study CT-P10 3.3.

Other clinical chemistry

For the rheumatoid arthritis studies, there were single cases of reduced serum potassium, sodium, calcium and glucose; as well as increases in serum sodium and creatinine phosphokinase distributed equally across the rituximab treatment groups. One fatal case of tumour lysis syndrome was reported in Study CT-P10 3.3 in a CT-P10 treated subject. In total, grade 4 hyperuricaemia was reported in 1 CT-P10 treated subject (1.4% of 70) and 3 Rituxan treated patients (4.3% of 70) in Study CT-P10 3.3. There were also single cases of reduced serum potassium, sodium and calcium; as well as increases in serum sodium and creatinine phosphokinase distributed equally across the two rituximab treatment groups in Study CT-P10 3.3.

Haematology and haematological toxicity

In the pooled analysis for the rheumatoid arthritis population (Studies CT-P10 1.1, 1.3 and 3.2), a similar proportion of patients between the treatment groups recorded neutropenia: 3.9% (11 of 283) of patients in the total CT-P10 group and 2.7% (7 of 262) of subjects in the reference rituximab cohort. Of those, serious or grade 3 (severe) AEs were reported in similar proportions of patients between the treatment groups: 2 (0.7%) and 3 (1.1%) patients in the total CT-P10 and reference rituximab groups, respectively (Table 7). In Study CT-P10 3.3, a higher proportion of patients in the CT-P10 group recorded neutropenia (35.7%; 25 of 70) compared to 25.7% (18 of 70) in the Rituxan group. However, there were no notable differences between the treatment groups with regard to the grade 3 or higher neutropenic AEs: 20 (16.9%) patients and 13 (12.9%) patients in the CT-P10 and Rituxan groups, respectively. Serious AEs were reported for 3 patients in each treatment group of Study CT-P10 3.3.

Table 7: Summary of neutropenic AEs 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=70)	(N=70)
Total number of events	12	11	51	35
Number (%) of patients ≥ 1 event	11 (3.9)	7 (2.7)	25 (35.7)	18 (25.7)
Number (%) of patients ≥ 1 serious event	0	2 (0.8)	3 (4.3)	3 (4.3)
Incidence rate in patients/100 PY (95 % CI)	3.9 (1.97 – 7.04)	3.0 (1.19 – 6.09)	78.7 (50.96 – 116.24)	56.8 (33.68 – 89.81)
Severity / Nature of risk				
Grade 1 (mild)	8 (2.8)	3 (1.1)	1 (1.4)	0
Grade 2 (moderate)	1 (0.4)	1 (0.4)	4 (5.7)	5 (7.1)
Grade 3 (severe)	2 (0.7)	3 (1.1)	15 (21.4)	8 (11.4)
Grade 4 (life-threatening)	0	0	5 (7.1)	5 (7.1)
Outcomes				
Recovered	11 (3.9)	7 (2.7)	24 (34.3)	18 (25.7)
Recovering	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.

PY: patient years

Other significant haematological AEs such as grade 3 or higher anaemia, lymphopenia or thrombocytopenia were rare AEs recorded throughout the studies and did not manifest a treatment related difference (in either the rheumatoid arthritis or lymphoma trials).

Serum immunoglobulin levels

Although rituximab induces B-cell depletion in the majority of patients, this effect is associated with decreased serum immunoglobulins in a minority of patients. Since B-cells are essential for humoral immunity, prolonged B-cell depletion may result in hypogammaglobulinaemia and increase the risk of infections (MabThera PI). Throughout the CT-P10 studies, mean changes from baseline in serum IgM, IgG and IgA levels were small at each time point and there were no notable differences between the treatment groups across the rheumatoid arthritis and NHL trials.

Electrocardiograph findings and cardiovascular safety

No clinically notable ECG findings following rituximab (any formulation) were reported throughout the CT-P10 clinical studies. In the clinical development program for CT-P10, the analysis of cardiovascular risks took into account AEs assigned to the SOCs of cardiac disorders and vascular disorders. When pooled across the CT-P10 studies conducted in rheumatoid arthritis patients (Studies CT-P10 1.1, 1.3 3.2), the proportion of patients who experienced at least 1 AE of cardiovascular disease were 10.2% (29 of 283) of patients in the total CT-P10 group and 7.3% (19 of 262) of subjects in the reference rituximab cohort.

Of those, AEs considered by the investigator to be related to rituximab were reported for 3 (1.1%) patients and 6 (2.3%) patients in the total CT-P10 and the reference rituximab group, respectively. There were 6 serious cardiovascular AEs in the CT-P10 group, each reported for 1 patient (2.1%), but all these events were considered by investigator to be unrelated to the study drug. These AEs include deep vein thrombosis, mitral valve prolapse, pericardial effusion and arrhythmia reported in Study CT-P10 1.1; and myocardial ischaemia and vena cava thrombosis reported in Study CT-P10 3.2.

The sponsor conducted a further evaluation of the slightly higher occurrence of cardiovascular AEs in the CT-P10 treated cohort and the analysis concluded that the observed differences may be due to the imbalance in baseline risk factors related to the cardiovascular disease. In the pooled rheumatoid arthritis population, a higher proportion of patients in the CT-P10 versus reference rituximab group had at least one risk factor for cardiovascular disease (55.8% (158 of 283) of patients in the total CT-P10 group versus 48.9% (128 of 262) of subjects in the reference rituximab cohort). In Study CT-P10 3.3, there was 1 treatment related case of deep vein thrombosis in a CT-P10 treated subject but no other noteworthy AEs.

Vital signs and clinical examination findings

In all of the CT-P10 clinical studies, the mean changes from baseline in vital signs were small with no apparent differences between the treatment groups. The most commonly reported clinically notable vital sign results from the start of the study drug infusion during monitoring were high respiratory rate, low respiratory rate and high diastolic blood pressure. These results were reported for approximately 10% of patients at several time points. However, there were no differences between the treatment groups in the proportions of patients with high or low respiratory rate, or high diastolic blood pressure.

In the CT-P10 clinical studies, physical examination findings were classified as either normal or abnormal. The majority of patients enrolled in each trial had normal baseline physical exam results that remained normal at each time point. There were no notable differences between the treatment groups. In Study CT-P10 1.3, physical examination was not performed regularly (as per the trial protocol), but patients were monitored for any new or worsened signs that were reported as AEs in the opinion of the investigator.

Immunogenicity and immunological events

Background and methods

In historical trials conducted with rituximab, the incidence of anti-human anti-chimeric antibodies (HACA; alternatively known as Anti-Drug Antibodies) was very low in patients with NHL compared to subjects with autoimmune disease. Using an ELISA assay, HACA was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving rituximab monotherapy. In various rheumatoid arthritis studies, the incidence of HACA to rituximab is up to 12.7% (typically 6 to 8% depending on assay). In patients receiving rituximab for ANCA associated vasculitis; HACA can be recorded in 23% of patients. The data indicates that the rheumatoid arthritis patient population is likely to be a more sensitive clinical model to assess the comparability of the immunogenicity profile of CT-P10 and reference rituximab drugs, than oncology patients.

The incidence of anti-drug antibodies depends on a number of factors, including disease state, type of assay, assay sensitivity and interference by free drug. Assays for anti-drug antibodies must also avoid interference by rheumatoid factor and heterophile antibody. The immunogenicity evaluation of CT-P10 was conducted using an appropriately developed and validated method of investigation, which was fittingly outlined in the submission. An ECL immunoassay to detect anti-drug antibodies against CT-P10 or reference rituximab in human serum was developed and validated as part of the drug development process. In Studies CT-P10 3.2 and CT-P10 3.3, the confirmatory and titration methods were improved by using of atumumab in order to reduce the potential for interference with circulating CD20 membrane fragments and thereby prevent binding of the CD20-related antigen in the sample to the labelled rituximab reagents in the assay. A complement-dependent cytotoxicity (CDC) assay was used as a second step to detect the neutralising activity of anti-drug antibodies (and its titre) against CT-P10 or the reference rituximab product in human serum.

Study CT-P10 3.2

In Study CT-P10 3.2, almost 10% of patients had a positive anti-drug antibodies result at baseline. At Week 24, a lower percentage of CT-P10 treated subjects had positive anti-drug antibodies (14.9%; 24 of 161) compared to the two reference rituximab drugs (26.7% (16 of 60) with MabThera and 21.9% (33 of 151) with Rituxan)(Table 8). At Week 48, 4.9% (7 of 161) of patients in the CT-P10 group and 9.2% (18 of 196) of subjects in the reference rituximab cohort, showed positive anti-drug antibodies results. Overall, the proportion of patients with positive anti-drug antibodies results was comparable between CT-P10 and the reference rituximab groups with a very low incidence of neutralising antibodies (neutralising antibodies) across the groups. Moreover, the mean anti-drug antibodies titre results were low and comparable between the treatment groups.

Table 8: Summary of anti-drug antibodies (ADA) and neutralising antibodies (Nab) Results in Study CT-P10 3.2 (2nd Treatment Course)

Immunogenicity Test	CT-P10 (N=161)	MabThera® (N=60)	Rituxan® (N=151)	MabThera® + Rituxan® (N=211)
	n (%)			
Week 0				
ADA Positive	19 (11.8%)	7 (11.7%)	13 (8.6%)	20 (9.5%)
NAb Positive (as % of ADA positive)	1 (5.26%)	0	0	0
Week 24				
ADA Positive	24 (14.9%)	16 (26.7%)	33 (21.9%)	49 (23.2%)
NAb Positive (as % of ADA positive)	0	0	1 (3.0%)	1 (2.0%)
Immunogenicity Test	**CT-P10 (N=142)**	**MabThera® (N=58)**	**Rituxan® (N=138)**	**MabThera® + Rituxan® (N=196)**
	n (%)			
Week 48				
ADA Positive	7 (4.9%)	5 (8.6%)	13 (9.4%)	18 (9.2%)
NAb Positive (as % of ADA positive)	1 (14.3%)	0	1 (7.7%)	1 (5.6%)

Study CT-P10 3.3

At baseline, 5 patients (7.1% of 70) in the CT-P10 group and 8 subjects (11.4% of 70) in the Rituxan arm had positive anti-drug antibodies (all of which were negative for neutralising antibodies). At core Cycle 4, 2 patients in the CT-P10 arm (2.9%) and 1 subject in the Rituxan group had positive anti-drug antibodies (all 3 cases were neutralising antibodies positive). At the end of study visit, 1 patient in each group was anti-drug antibodies positive (with only the Rituxan treated subject being neutralising antibodies positive). Overall, no significant differences in anti-drug antibodies and neutralising antibodies status were observed in Study CT-P10 3.3 up to 24 weeks.

Supporting rheumatoid arthritis studies

At baseline in Study CT-P10 1.1, there was a relatively high and similar incidence of positive anti-drug antibodies between the CT-P10 and MabThera groups which did not appreciably increase in frequency following a second rituximab treatment course in main study period (up to core Week 48) or the extension study period (up to Week 24) (Table 9). In addition, antibody titre analyses highlighted a slight trend towards increased antibody titres with the number of rituximab doses received, although this trend was less apparent in the extension phase. In Study CT-P10 1.3, 13.2% (5 of 38, 1 neutralising antibodies positive) of patients in the CT-P10 maintenance group and 15.0% (3 of 20) of subjects in the CT-P10 switch treatment cohort recorded positive anti-drug antibodies at Week 24.

Table 9: Summary of anti-drug antibodies (ADA) and neutralising antibodies (Nab) Results in Study CT-P10 1.1

Visit / Result	All Safety Population	
	CT-P10 1000mg (N=102)	MabThera® 1000mg (N=51)
	n/N[1] (%)	
Core Week 0		
ADA Positive	23/102 (22.5)	7/51 (13.7)
NAb Positive (as % of ADA positive)	6/23 (26.1)	0
Core Week 8		
ADA Positive	1/99 (1.0)	0/48
NAb Positive (as % of ADA positive)	1/1 (100)	0
Core Week 16		
ADA Positive	8/97 (8.2)	1/48 (2.1)
NAb Positive (as % of ADA positive)	1/8 (12.5)	0
Core Week 24		
ADA Positive	18/95 (18.9)	9/46 (19.6)
NAb Positive (as % of ADA positive)	2/18 (11.1)	1/9 (11.1)
Core Week 32		
ADA Positive	28/80 (35.0)	19/41 (46.3)
NAb Positive (as % of ADA positive)	2/28 (7.1)	1/19 (5.3)
Core Week 40		
ADA Positive	30/62 (48.4)	18/32 (56.3)
NAb Positive (as % of ADA positive)	2/30 (6.7)	3/18 (16.7)
Core Week 48		
ADA Positive	12/32 (37.5)	10/22 (45.5)
NAb Positive (as % of ADA positive)	1/12 (8.3)	1/10 (10.0)

Table 10: Summary of anti-drug antibodies (ADA) and neutralising antibodies (Nab) Results in Study CT-P10 1.3

Visit / Result	CT-P10 1000 mg (N'=60)	MabThera® 1000 mg (N'=23)
	n/N'[1] (%)	
Extension week 0		
ADA Positive	27/60 (45.0)	10/22 (45.5)
NAb Positive (as % of ADA positive)	2/27 (7.4)	1/10 (10.0)
Extension Week 8		
ADA Positive	1/59 (1.7)	0/21
NAb Positive (as % of ADA positive)	1/1 (100)	0
Extension Week 16		
ADA Positive	5/59 (8.5)	1/21 (4.8)
NAb Positive (as % of ADA positive)	2/5 (40.0)	0
Extension Week 24		
ADA Positive	12/58 (20.7)	5/20 (25.0)
NAb Positive (as % of ADA positive)	1/12 (8.3)	1/5 (20.0)

Serious skin reactions

There were no AEs of Stevens - Johnson syndrome or Toxic Epidermal Necrolysis reported throughout the studies with CT-P10, although this has been reported as a rare event with rituximab.

Other safety issues

No documented pregnancies were reported in the CT-P10 studies included in this submission. According to the MabThera PI, there are no important intrinsic and extrinsic factors (including age, gender and ethnicity) that significantly alter the safety profile of rituximab. However, the extent of prior immunosuppression is an important factor which needs to be considered in the context of risk of infections, particularly opportunistic infections such as progressive multifocal leukoencephalopathy (PML) during rituximab therapy. All rheumatoid arthritis patients in the CT-P10 studies received concomitant low dose weekly methotrexate and had prior exposure to at least one anti-TNF drug (consistent with the approved MabThera treatment indication in rheumatoid arthritis). In Study CT-P10 3.3, all subjects received concurrent chemotherapy with CVP as per the MabThera approved oncology treatment indication.

In all of the CT-P10 clinical studies, the majority of patients had normal chest x-rays at each time point and there were no positive tuberculosis results reported except for 1 patient who received Rituxan treatment in Study CT-P10 3.3. This patient has a history of latent tuberculosis and was diagnosed with reactivation of tuberculosis based on the CT scan at the core Cycle 5 visit. The AE was regarded as a non-serious, grade 2 (moderate) event of tuberculosis which recovered without sequelae but resulted in permanent discontinuation from the study treatment.

Post-marketing data

Not applicable as CT-P10 has not been marketed in any country as yet. However, there is a large volume of long term clinical experience with MabThera and Rituxan in the requested treatment indications to indicate that if CT-P10 meets the criteria for biosimilarity with MabThera (reference product in Australia), then a predictable positive benefit: risk assessment can be concluded.

Evaluator's conclusions on safety

The safety profile of rituximab is well characterised in the published literature. In this submission for the registration of CT-P10 (biosimilar medicine of MabThera and Rituxan), the principal safety population consisted of 666 adult patients with either active rheumatoid arthritis or advanced follicular lymphoma who received at least one full or partial dose of either CT-P10 or reference rituximab during the Phase I to III clinical trials. Of these, 354 patients were exposed to CT-P10 (average of two infusion courses for a median follow-up period of 48 weeks) and 332 subjects were given reference rituximab (either MabThera or Rituxan) on a similar number of occasions and duration of follow-up. Included in the above exposure, 20 subjects with rheumatoid arthritis were exposed to both MabThera and CT-P10 in the open label, treatment maintenance Study CT-P10 1.3 (single 1–way switch in rituximab formulations). Overall, the size of the safety population and the duration of exposure to CT-P10 meet the regulatory guidelines[13] for presenting a safety population of sufficient size and follow-up duration to assess for possible registration.

Rheumatoid arthritis

The overall safety profile of CT-P10 appears to be similar to that of the reference rituximab drugs with the pooled incidences of overall AEs (67.2 to 70.3%) and SAEs (8.8 to 10.2%) in the rheumatoid arthritis population (that is, by combining data from Studies CT-P10 1.1, 1.3 and CT-P10 3.2) being equivalent although slightly lower with reference rituximab. In the rheumatoid arthritis studies, the most common reported types of AEs were infections (similar frequency with 36.0% in the total CT-P10 group versus 34.7% in the reference rituximab arm) and infusion related reactions. The two most common sites of infection were the upper respiratory and urinary tract. In addition, approximately 6% of

all subjects recorded lower respiratory tract infection, regardless of which rituximab treatment they received.

The overall incidence of infusion related reaction was consistently higher (approximately two fold) in CT-P10 treated subjects versus MabThera or Rituxan treated patients in Studies CT-P10 1.1 and CT-P10 3.2. The overall frequency of treatment related AEs was also comparable between the CT-P10 and reference rituximab treatment groups in the pooled rheumatoid arthritis population. However, a higher incidence of treatment related infusion related reactions were reported with CT-P10 (16.6%) versus reference rituximab (10.7%). In the pooled rheumatoid arthritis dataset, the frequency of patients who discontinued due to drug-related AEs was low and similar between the treatment cohorts (3.2 to 5.0% at 48 weeks) with the most frequent type of AE leading to permanent study treatment discontinuation being infusion related reaction (4 patients in each treatment group CT-P10 versus reference rituximab).

One CT-P10 treated subject died during Study CT-P10 3.2 of suspected right brachial vein thrombosis and cellulitis approximately 7 weeks after receiving her initial course of CT-P10. Across the CT-P10 studies conducted in rheumatoid arthritis patients (Studies CT-P10 1.1, 1.3 3.2), the proportion of patients who experienced at least 1 AE of cardiovascular disease was numerically higher in the total CT-P10 group at 10.2% (29 of 283) versus 7.3% (19 of 262) of subjects in the reference rituximab cohort. The sponsor explained this observation as being related to CT-P10 recruited patients having a higher frequency of cardiovascular risk factors.

The most commonly reported laboratory abnormality was neutropenia. In the pooled analysis for the rheumatoid arthritis population (Studies CT-P10 1.1, 1.3 and 3.2), a similar proportion of patients between the treatment groups recorded neutropenia: 3.9% (11 of 283) of patients in the total CT-P10 group and 2.7% (7 of 262) of subjects in the reference rituximab cohort. The incidence of subjects developing anti-drug antibodies was comparable between CT-P10 and reference rituximab, and the clinical relevance of anti-drug antibodies is yet to be fully defined with no discernible link to the risk of infection, infusion related reaction or any other significant safety concern. By Week 24 in Study CT-P10 3.2, there was an equivalent rate of positive anti-drug antibodies results in the CT-P10 group (14.9%; 24 of 161) compared to reference therapy (23.2%; 49 of 211). In addition, anti-drug antibodies positive subjects rarely tested positive for neutralising antibodies.

In the 20 subjects who have switched from MabThera to CT-P10 in Study CT-P10 1.3, there is no overt change to the safety profile of CT-P10 regarding the incidence and types of AEs. However, the very small sample size of the single 1-way rituximab switch cohort at present limits the external validity of the observation and will require ongoing pharmacovigilance.

Advanced follicular lymphoma

The safety dataset in patients with advanced follicular lymphoma is preliminary and limited to 24 weeks of treatment follow-up in 140 subjects (70 patients in each treatment group), so there are limitations to reaching definitive conclusions about the safety profile of CT-P10 in the oncology treatment setting. Similar proportions of subjects in each treatment group (CT-P10 and Rituxan) reported AEs (80.0 to 82.9%) and treatment related AEs (48.6 to 52.9%). The most frequently reported AEs in the CT-P10 treatment group were neutropenia (24 (34.3%) patients) followed by infusion related reaction (16 (22.9%) patients) and constipation (12 (17.1%) patients). The majority of AEs were of CTCAE (common terminology criteria for adverse events) grade 1 or 2 intensity, however, 1 grade 5 AE of tumour lysis syndrome was reported in a patient treated with CT-P10. Again, neutropenia and infusion related reactions were reported in a higher number of CT-P10 versus Rituxan treated subjects in Study CT-P10 3.3. The incidence of SAEs during the core study period was higher for CT-P10 (16 (22.9%) patients) compared with Rituxan

(9 (12.9%) patients), but the frequency of treatment related SAEs was similar in the two treatment groups (6 (8.6%) patients and 4 (5.7%) patients in the CT-P10 and Rituxan treatment groups, respectively). AEs leading to permanent study drug discontinuation up to Week 24 was also slightly higher for CT-P10 (5 (7.1%) patients versus 1 (1.4%) 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 CT-P10 and Rituxan treatment groups, respectively. One patient treated with CT-P10 discontinued early due to infusion related reaction and had a positive result for anti-drug antibodies and neutralising antibodies tests at core Cycle 4.

Neutropenia was the most common CTCAE grade 3 or higher laboratory abnormality during the core study period in both treatment groups. CT-P10 treated subjects had a higher rate of grade 3 neutropenia (14 (20.0%) patients versus 9 (12.9%) patients in the Rituxan arm). However, grade 4 neutropenia affected 5 (7.1% of 70) patients in each group. The majority of patients had negative results for anti-drug antibodies and neutralising antibodies tests during the core study period. The proportion of patients with positive anti-drug antibodies results was similar in the two treatment groups up to Week 24 (3 patients and 2 patients in the CT-P10 and Rituxan treatment groups, respectively). Mean IgM, IgG and IgA levels decreased from baseline through to Cycle 8, and there were no notable differences between the two treatment groups for this parameter.

Conclusion

In conclusion, the available safety data in this submission is supportive of the sponsor claim of biosimilarity between CT-P10 and MabThera. The frequencies and nature of the AEs were in line with those reported for the originator rituximab product (MabThera or Rituxan) in the rheumatoid arthritis and NHL study populations. No new safety signals have emerged from the submitted dataset to indicate the known risk profile of rituximab has altered. The current safety dataset for CT-P10 is limited to 24 to 48 weeks of treatment follow-up in the majority of studied subjects, and it would be important to continue collecting data beyond this time frame. Nonetheless, the safety data for rituximab exceeds 18 years of treatment follow-up and it is likely that CT-P10 will demonstrate a similar safety profile over longer term follow-up based on the similar short term safety experience between the formulations of rituximab. However, the CT-P10 studies recruited subjects with active rheumatoid arthritis or lymphoma who were meticulously screened for risks of immunosuppression, and it is unclear if all formulations of rituximab will demonstrate a similar safety profile in all of the patient populations for which MabThera is currently approved. Moreover, additional safety data from the maintenance study phase of Study CT-P10 3.3, the planned extension period of Study CT-P10 3.2 and the planned new trial in patients with low tumour burden lymphoma (Study CT-P10 3.4) will provide important, additional long term safety data.

First round benefit-risk assessment

First round assessment of benefits

Table 11: First round assessment of benefits

Indications: rheumatoid arthritis, NHL, CLL and ANCA associated systemic vasculitis	
Benefits	**Strengths and Uncertainties**
CT-P10 results in a clinically significant	Observed data in the Phase III Study CT-P10

Indications: rheumatoid arthritis, NHL, CLL and ANCA associated systemic vasculitis	
Benefits	**Strengths and Uncertainties**
improvement in rheumatoid arthritis disease activity (as measured by the mean change from baseline over 24 to 48 weeks in DAS28 score-CRP or ESR) that is comparable to MabThera and Rituxan.	3.2 as well as the Phase I Study CT-P10 1.1. Over 24 weeks, there is a mean decrease in DAS28-CRP by 2.3 units (from a baseline level of 5.8), which is consistent with the historical data for rituximab.
CT-P10 produces improvements in the signs and symptoms of active rheumatoid arthritis (as per the ACR20, 50 and 70 response rates) that is comparable to MabThera.	Observed data in the Phase III trial – Study CT-P10 3.2 and CT-P10 1.1. The magnitude of benefit is clinically meaningful and consistent with the historical rituximab response rate.
Time to onset of response in active rheumatoid arthritis was timely and slightly shorter (although equivalent statistically) to reference rituximab, however, time to re-treatment may be slightly earlier with CT-P10.	Observed data in the Phase I Study CT-P10 1.1 and the ensuing open label treatment maintenance trial (Study CT-P10 1.3). The clinical significance of this finding is unclear.
Persistence of clinical response for up to 104 weeks in the subgroup of rheumatoid arthritis patients who are tolerating and responding to intermittent rituximab infusions (for example, ACR20 response rate of 55 to 58% at Week 24 after re-treatment).	Observed data in open label, maintenance Study CT-P10 1.3. Limited long term trial data has been provided but should be available in the future. Follow-up to 52 weeks of treatment provides medium term experience but multi-year (≥ 2 years) follow-up is preferential.
Convenient schedule and administration mode (IV infusion at regular or intermittent intervals depending on the treatment indication).	Supported by robust pharmacokinetics and pharmacodynamic data in both the rheumatoid arthritis and oncology setting.
High rates of overall disease response (> 80%) in advanced follicular lymphoma which is comparable with Rituxan therapy.	Supported by the Phase III clinical study CT-P10 3.3 (limited to 24 weeks of treatment follow-up which is a relative deficiency).
Alternative formulation of rituximab to treat various autoimmune inflammatory disorders, which are significantly prevalent in Australia.	Sound formulation development program. No direct evidence of clinical efficacy in ANCA vasculitis and CLL treatment indications, but sponsor provided justification for extrapolation of adult treatment indications from current dataset.
Comparable pharmacokinetics and pharmacodynamic data for CT-P10 versus reference rituximab in two treatment settings (rheumatoid arthritis as an autoimmune model and oncology).	Three well-designed studies collected pharmacokinetics data in the development program (Studies CT-P10 1.1, CT-P10 3.2 and CT-P10 3.3).

First round assessment of risks

Table 12: First round assessment of risks

Risks	Strengths and Uncertainties
Increased incidence of overall and serious infection with CT-P10 which is comparable to that observed with MabThera.	Observed data in all four of the clinical studies with CT-P10 included in this submission. Despite meticulous screening and observation, serious infection ~ 5% of subjects in each rituximab treatment group.
Increased incidence of infusion related reactions with CT-P10 that is about double the rate of reference rituximab	Observed data in the Phase III rheumatoid arthritis Study CT-P10 3.2 and Study CT-P10 1.1 (in rheumatoid arthritis) as well as Study CT-P10 3.2 (in lymphoma).
Low incidence of permanent treatment discontinuations due to AEs with CT-P10 that is comparable with MabThera.	This was observed in the Phase I to III clinical studies.
Increased incidence of neutropenia with CT-P10 versus reference rituximab products in both rheumatoid arthritis and lymphoma.	Observed in Phase I to III clinical trials. This is known safety information which is included in the proposed PI and RMP for CT-P10.
Comparable (but relatively low) rates of anti-drug antibody formation with CT-P10 and reference rituximab suggesting equivalence in immunogenicity.	This was consistently observed in the Phase I and III clinical studies in which anti-drug antibodies was assessed. Study CT-P10 3.3 (NHL) had much lower rates of anti-drug antibodies than the rheumatoid arthritis studies, which is consistent with literature about anti-drug antibodies formation.
CT-P10 has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction, those with concurrent Hepatitis B or C virus or HIV, and in pregnant/lactating women.	The populations with inadequate clinical data regarding CT-P10 therapy are appropriately identified in the proposed RMP.

First round assessment of benefit-risk balance

The submission indicates that the benefit-risk balance of CT-P10 is favourable for the treatment of active rheumatoid arthritis in adult patients, who have had an inadequate response to treatment with methotrexate and anti-TNF therapy (Studies CT-P10 1.1 and CT-P10 3.2). The currently available dataset on the benefit-risk balance of CT-P10 in adult patients with rheumatoid arthritis is limited to 102 weeks of treatment follow-up in a relatively small number of subjects beyond 48 weeks of treatment follow-up. However, this submission also contains a sufficient volume of data to support the claim that CT-P10 is pharmacokinetically equivalent to the reference product, MabThera, in adult patients with active rheumatoid arthritis (Studies CT-P10 1.1 and CT-P10 3.2) and in those with lymphoma (Study CT-P10 3.3).

The sponsor has provided a review of the literature on the role of B-cells in the disorders covered by the therapeutic indications of MabThera and the primary mechanism by which rituximab exerts its clinical efficacy. The mechanism of action of rituximab is complex but

the primary mode of action results from B-cell mediated biological activities. Rituximab is a recombinant chimeric monoclonal antibody that produces B-cell lysis, thereby reducing the production of pro-inflammatory cytokines and a reduction in T-cell activation. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from rheumatoid arthritis to ANCA vasculitis. In addition, the sponsor has provided justification for the extrapolation of treatment indications for CT-P10 to include that which are approved for MabThera on the basis of biosimilarity. Extrapolation of the pharmacokinetic, efficacy and safety data generated in the four trials in this submission which examined adult patients with rheumatoid arthritis and follicular lymphoma is justifiable on the basis of the results of the pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the rituximab molecule). Despite sharing similar and overlapping pathophysiological immunological mechanisms, rheumatoid arthritis is considered the primary clinical disease model of moderate sensitivity for assessing the efficacy and safety of CT-P10 in autoimmune disease as well as lymphoid-based malignancies.[17]

On the safety aspect, there is an increased risk of infection (overall and serious) with CT-P10, which appears to be comparable to MabThera. The submitted studies show a potential increased risk of acute infusion reactions with CT-P10 compared to reference rituximab therapies. There are limitations to the current dataset, which will require ongoing pharmacovigilance. The efficacy and safety of CT-P10 in patients at a high risk of infection is not established. In addition, there is limited information about the safety and efficacy of switching to CT-P10 from previous MabThera therapy, or vice versa.

First round recommendation regarding authorisation

The clinical reviewer recommends acceptance of the sponsor's proposed registration of CT-P10 for all of the current approved treatment indications for MabThera in adult patients including rheumatoid arthritis, NHL, CLL and ANCA associated vasculitis. The current submission provides evidence that CT-P10 is therapeutically equivalent to reference rituximab formulations (MabThera and Rituxan) in improving the signs and symptoms of active rheumatoid arthritis in adult patients with active rheumatoid arthritis that are inadequately responding to methotrexate and have failed at least 1 previous anti-tumour necrosis factor (TNF) drug. Furthermore, CT-P10 demonstrates comparable efficacy and safety to Rituxan in treating patients with advanced follicular lymphoma in combination with conventional chemotherapy. The target treatment populations examined in the CT-P10 clinical studies are consistent with the approved treatment populations for MabThera. In addition, the applicant has provided data and a literature review assessment justifying the extrapolation of treatment indications to the other approved treatment indications for MabThera.

Should approval of the sponsor's proposed registration of CT-P10 be granted, approval should be subject to:

- Satisfactory response to the questions below,
- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study reports for the two on-going Phase III studies (CT-P10 3.2 and CT-P10 3.3) as well as the interim and final data for Study CT-P10 3.4 (proposed Phase III trial in patients with low tumour burden follicular lymphoma).

[17] Lee H. Is Extrapolation of the Safety and Efficacy Data in One Indication to Another Appropriate for Biosimilars? *The AAPS Journal* 2013; 16: 22-26

Clinical questions and second round evaluation

The sponsor's response dated October 27, 2017 addresses four questions that were raised in the first round clinical assessment.

Pharmacodynamics

Question 1

Could the sponsor comment on the clinical significance of earlier B-cell recovery observed with CT-P10 in the rheumatoid arthritis studies and in particular, how that may affect the frequency of re-treatment and disease control.

Sponsor response:

The applicant provided several post-hoc analyses examining the earlier B-cell recovery and earlier re-treatment with CT-P10 group in Study CT-P10 1.1, and concluded that there was no evidence to suggest that the duration of action of CT-P10 is significantly different from that of MabThera.

In Study CT-P10 1.1, patients who met either of the following criteria were eligible for re-treatment: when residual disease activity remained after the first dose in the core study period, or when disease activity returned within 40 weeks from the first dose date in the core study period. However, once a patient met the criteria for re-treatment (that is, second treatment course in the extension study period), it was at the investigator's discretion. In addition to this, B-cell or IgM levels were assessed to check whether a second treatment course could be administered without safety problems. This was defined as the result for serum B-cell or IgM values being greater than the lower limit of normal or at least 50% of the baseline reading.

In Study CT-10 1.1, the proportion of subjects (64.7%) who became eligible for re-treatment was identical in each treatment group (66 of 102 in the CT-P10 group and 33 of 51 in the MabThera arm). Among these patients, the percentage who actually received a second course of rituximab was higher in the CT-P10 group (52.9% (54 of 102) versus 43.1% (22 of 51) in the MabThera arm). As such, a higher proportion of subjects in the MabThera group were not re-treated as per the investigator's decision, and this explains the difference in re-treatment rates between the 2 groups (11.8% (12 of 102) of patients in the CT-P10 group and 21.6% (11 of 51) of patients in the MabThera arm). The treatment blind was maintained and inquiry of the individual cases confirmed that there was no bias during these decisions. Table 13 provides a summary of the eligibility for re-treatment with rituximab data in Study CT-P10 1.1.

The sponsor has also investigated those patients who were eligible for, but not re-treated with rituximab. In both treatment groups of Study CT-P10 1.1, the most common reason was maintenance of good response (according to the Visual analog scale (VAS) for pain and Health assessment questionnaire (HAQ)) which occurred in 7.8% (8 of 102) of patients in the CT-P10 group and 9.8% (5 of 51) of subjects in the MabThera arm. Two patients in each group experienced infusion related reactions that resulted in no re-treatment being offered, 1 subject in the CT-P10 group terminated early due to no clinical efficacy, 1 patient in the MabThera arm terminated early due to consent withdrawal and another subject in the MabThera group experienced an AE of infection. For 3 subjects (2 in the MabThera arm and 1 in the CT-P10 group) no obvious factor could be identified for them not receiving re-treatment with rituximab, although the patients were eligible.

In addition, the sponsor has analysed the time to re-treatment with rituximab in Study CT-P10 1.1 (using Kaplan Meier analysis of the all randomised cohort) based on an assumption that all patients who met the eligibility criteria for re-treatment as per protocol were re-treated regardless of the actual treatment (referred to as the 'time to

eligibility for re-treatment'). In the analysis, the time to eligibility for re-treatment as per protocol was similar between the two groups (median of 40.1 weeks (25th and 75th percentile of 32.3 and 48.1 week) in the CT-P10 group, and median of 40.1 weeks (25th and 75th of 32.4 and 48.4 weeks) in the MabThera arm).

Table 13: Eligible for re-treatment and actual re-treatment data in Study CT-P10 1.1

Number of Patients (%)	CT-P10 1000 mg (N=102)	MabThera® 1000 mg (N=51)	Total (N=153)
Eligible subjects for the 2nd treatment course (Extension Study Period)	**66/102 (64.7)**	**33/51 (64.7)**	**99/153 (64.7)**
Retreated (Entered Extension Study Period)	54/102 (52.9)	22/51 (43.1)	76/153 (49.7)
Not retreated (Did not enter Extension Study Period)	12/102 (11.8)	11/51 (21.6)	23/153 (15.0)
Ineligible subjects for the 2nd treatment course	28/102 (27.5)	12/51 (23.5)	40/153 (26.1)

Note: Eligibility for retreatment was determined according to protocol. Subjects whose eligibility could not be confirmed for the following reasons were excluded from the table (8 [7.8%] patients in CT-P10, 6 [11.8%] patients in MabThera® groups, separately).

a. Early discontinuation before Week 16: 5 patients (0111-1001, 0204-1001, 0304-1001, 0604-1001, 0806-1012) in CT-P10, 3 patients (0108-1001, 0208-1001, 0610-1002) in MabThera® groups, separately;
b. No additional DAS28 results assessed after best DAS28 due to early termination: 3 patients (0201-1004, 0209-1001, 0803-1001) in CT-P10, 2 patients (0601-1002, 0803-1011) in MabThera® groups, separately;
c. Unable to assess EULAR response between Week 16-24 due to omission of GH (Patient's Global Assessment of Disease Activity measured on the Visual Analogue Scale (mm)) results at baseline: 1 patient (0304-1007) in MabThera® group.

The sponsor has also provided efficacy data on the re-treatment population of Study CT-P10 1.1 up to core Week 48. This shows comparable mean changes from baseline in the DAS28 scores (measured by ESR or CRP) for the two re-treatment groups.

In Study CT-P10 1.1, B-cell count recovery (defined as greater than or equal to the lower limit of normal or at least 50% of the baseline value) occurred earlier in more patients in the CT-P10 group compared to the MabThera arm. The data on B-cell recovery in Study CT-P10 1.1 is:

- 7.7% (7 of 91) and 2.4% (1 of 41) patients in CT-P10 and MabThera groups at core Week 24,
- 13.7% (10 of 73) and 8.3% (3 of 36) patients in CT-P10 and MabThera arms at core Week 32,
- 24.1% (14 of 58) and 20.7% (6 of 9) patients in CT-P10 and MabThera arms at core Week 40, and
- 33.3% (10 of 30) and 47.4% (9 of 19) patients in CT-P10 and MabThera groups at core Week 48.

The sponsor asserts that the small differences observed in Study CT-P10 1.1 should be viewed with caution due to the small patient numbers and the exclusion of re-treated patients from the calculations. The sponsor examined whether any small differences in B-cell kinetics could be identified in any of the other CT-P10 studies. An analysis of B-cell kinetics was also carried out in Study CT-P10 3.2 which defined B-cell recovery as B-cell count greater than or equal to the lower limit of normal or at least 50% of the baseline value, assessed at Week 24 and Week 48. Study CT-P10 3.2 did not find any significant differences between CT-P10, MabThera and Rituxan for B-cell recovery.

The data on B-cell count recovery in Study CT-P10 3.2 is:

- 4.1% (5 of 121) and 3.6% (6 of 165) patients in CT-P10 and reference rituximab groups at Week 24,
- 3.4% (4 of 117) and 1.9% (3 of 154) patients in CT-P10 and reference rituximab arms at Week 48.

The applicant also included historical data for comparison and provided literature indicating that no conclusive relationship has been established between the degree of B-cell depletion and the durability of efficacy, or safety findings. In MabThera rheumatoid arthritis studies, B-cell depletion was maintained over 24 weeks in the majority with only a small proportion of patients (5.9%) showing signs of peripheral B-cell recovery (that is, B-cell count above the lower limit of normal, 80 cells/μL) by Week 24[18] which is consistent with what has been observed in the CT-P10 treatment groups of Studies CT-P10 1.1 (7.7%) and CT-P10 3.2 (4.1%).

The applicant has also provided additional analyses of the CT-P10 rheumatoid arthritis studies using a Cox proportional hazards model to investigate the potential impact of B-cell recovery upon efficacy outcome. In Study CT-P10 1.1, the estimated hazard ratio of the response variable, decrease in European League against rheumatism (EULAR) CRP was 1.01 (95% CI 0.99 to 1.03) with a p-value of 0.4856 for the duration of time of B-cell count below the lower limit of quantitation. The result indicates that the decrease in EULAR (CRP) was not correlated with the duration of time of B-cell count below the lower limit of quantitation. For the EULAR (ESR), the estimate of the hazard ratio was 1.00 (95% CI 0.98 to 1.02) with p-value = 0.7269, indicating there is no statistically significant correlation between the decrease in EULAR (CRP, ESR) and the duration of time of B-cell count below the lower limit of quantitation. In Study CT-P10 3.2, the results also demonstrate that there is no correlation between the duration of B-cell depletion and the time to decrease in EULAR response (both CRP and ESR).

In summary, the sponsor asserts that the apparent earlier B-cell count recovery and earlier re-treatment with CT-P10 observed in Study CT-P10 1.1 is not being driven by differences in efficacy between the two rituximab formulations. The totality of evidence shows no consistent trend for earlier B-cell recovery with CT-P10 compared with reference rituximab, and there is no clear link between B-cell recovery and therapeutic effect. Additionally, the sponsor says that it has shown that there is no evidence for diminished longer term efficacy outcomes in CT-P10 patients who remain untreated.

Evaluator comment:

The sponsor has provided a clear and valid explanation for the higher rate of re-treatment with CT-P10 versus MabThera observed in Study CT-P10 1.1, which was a consequence of investigator discretion (as per the trial protocol) rather than being reflective of any significant clinical difference between the two studied rituximab formulations. In particular, the proportion of protocol defined subjects eligible for re-treatment in Study CT-P10 1.1 was identical (at 64.7%) between the two treatment groups. Furthermore, the applicant has provided clinical efficacy data (mean change from baseline in DAS28 score as measured by ESR and CRP; at Weeks 32, 40 and 48) in the re-treatment population of Study CT-P10 1.1, which does not show any clinically significant difference in clinical response between the two treatment groups (CT-P10 and MabThera).

The sponsor also contained data showing that B-cell recovery kinetics in the rheumatoid arthritis studies (CT-P10 1.1 and 3.2) were similar between CT-P10 and reference

[18] EMA/717652/2010: Assessment Report For Mabthera (rituximab) Procedure No.: EMEA/H/C/000165/II/0065

rituximab formulations, as well as being consistent with published historical data. This data is reassuring with respect to the claim of biosimilarity.

The sponsor has also provided data (historical and directly with CT-P10) to indicate that there is discernible correlation between B-cell kinetics (namely, recovery of cell counts) and clinical efficacy, which supports the regulatory requirements for the authorisation of biosimilar rituximab.

Efficacy

Question 2

Could the sponsor provide the source information (for example, primary data in a tabulated format) on the x-ray results reported for Study CT-P10 1.1 as this could not be retrieved from the electronic submission document?

Sponsor response (Initial):

The sponsor has provided a tabulated summary of the radiographic data (modified Total Sharp Score (mTSS) and its components Erosion score (ES) and Joint space narrowing (JSN) score) for each treatment group in Study CT-P10 1.1. Table 14 displays the x-ray data for interpretation (efficacy population of Study CT-P10 1.1).

Table 14: Radiographic data at Core Week 48 and Extension Week 24 for Study CT-P10 1.1

		Total Erosion Score				Total Joint Space Narrowing Score				Total mTSS			
		CT-P10 1000 mg (N=100)		MabThera 1000 mg (N=48)		CT-P10 1000 mg (N=100)		MabThera 1000 mg (N=48)		CT-P10 1000 mg (N=100)		MabThera 1000 mg (N=48)	
Visit	Statistic	Actual Result	Change From Baseline	Actual Result	Change From Baseline	Actual Result	Change From Baseline	Actual Result	Change From Baseline	Actual Result	Change From Baseline	Actual Result	Change From Baseline
Baseline	n	91		45		91		45		91		45	
	Mean	55.94		46.71		51.09		46.11		107.03		92.82	
	SD	58.971		42.833		32.770		29.555		90.893		71.387	
	Minimum	2.5		4.5		13.5		8.0		19.0		12.5	
	Median	34.50		31.00		39.00		35.50		74.00		66.50	
	Maximum	248.0		149.5		149.0		114.5		397.0		255.0	
Core Week 48	n	22	21	17	17	22	21	17	17	22	21	17	17
	Mean	52.75	0.64	46.56	1.82	47.23	0.33	41.76	0.97	99.98	0.98	88.32	2.79
	SD	58.124	1.682	42.164	2.518	33.636	0.730	31.314	1.430	91.097	1.990	72.424	3.779
	Minimum	2.5	-1.0	5.5	0.0	17.0	-1.5	8.5	-0.5	19.5	-2.5	15.0	-0.5
	Median	30.50	0.00	25.50	1.50	32.25	0.50	29.00	0.50	58.75	0.50	54.00	2.00
	Maximum	234.5	7.0	142.0	11.0	149.0	1.5	115.0	5.0	383.5	7.5	257.0	16.0
Extension Week 24	n	49	46	17	16	49	46	17	16	49	46	17	16
	Mean	60.93	3.17	53.44	1.13	55.09	1.89	51.79	0.31	116.02	5.07	105.24	1.44
	SD	57.473	7.308	59.104	0.992	31.781	4.332	35.227	0.680	88.007	11.360	93.495	1.263
	Minimum	6.5	-1.0	7.5	-1.0	12.0	-1.0	16.5	-0.5	18.5	-1.5	24.5	-1.0
	Median	43.00	1.00	35.50	1.00	43.50	0.50	46.00	0.00	83.50	1.50	75.00	1.25
	Maximum	234.5	45.0	237.5	3.0	135.5	22.0	148.0	2.0	362.5	67.0	385.5	3.5

Evaluator comment (Initial):

Study CT-P10 1.1 demonstrated that joint damage progression (as measured by the total mTSS score) increased from baseline to Week 48 in the core study period (mean increase of 0.98 to 2.79 sharp units, but the absolute mean scores are lower at Week 48 than baseline), and to Week 24 in the extension study period for both treatment groups (mean increase 1.44-5.07 sharp units, which appears to be a clinically significant difference over 72 weeks) with the sponsor report stating that "*no clinically significant difference in joint damage progression seen between the two treatment groups*" (CT-P10 versus MabThera). No pair-wise statistical comparison has been provided to justify that conclusion, and the results for total mTSS and each of its components appear to be discrepant at each time point, without any explanation from the applicant.

Moreover, the baseline total mTSS in both treatment groups enrolled into Study CT-P10 1.1 are historically high at 92.82 to 107.03 sharp units. In Australia, it would be expected that patients with similar qualifying demographic characteristics would have total mTSS scores of approximately 20 to 30 sharp units. The sponsor needs to provide a detailed

explanation of x-ray dataset in Study CT-P10 1.1 including the potential limitations and their interpretation.

Sponsor response (follow-up):

During the course of the second round evaluation process, the applicant was asked by the TGA delegate to provide further comment on the radiographic data from Study CT-P10 1.1. The additional information and commentary is dated 24 November 2017.

The sponsor reports that it reviewed the x-ray data again and confirms there are no calculation errors. In both treatment groups of Study CT-P10 1.1, more than half of the patients assessed at baseline did not have radiographic data at core Week 48. At extension Week 24, about half of CT-P10 treated subjects (46 of 91) had baseline and follow-up x-rays for assessment, and just more than one third of MabThera treated subjects (16 of 45) had evaluable x-rays at both time points. In follow-up response, the sponsor has provided an additional analysis consisting of subjects who had x-ray results for both baseline and core Week 48, or extension Week 24. For CT-P10 treated subjects with baseline and Week 48 results, the mean mTSS was 93.17 at baseline and 94.14 at Week 48 (mean change in mTSS of 0.98). For MabThera treated patients with baseline and Week 48 results, the mean mTSS was 85.53 at baseline and 88.32 at Week 48 (mean change in mTSS of 2.79). For CT-P10 treated subjects with baseline and extension Week 24 results, the mean TSS was 112.86 at baseline and 117.92 at extension Week 24 (mean change in mTSS of 5.07). For MabThera treated patients with baseline and extension Week 24 results, the mean TSS was 86.28 at baseline and 87.72 at Week 48 (mean change in mTSS of 1.44). Overall, the sponsor asserts that the means of actual results and change from baseline over both time periods (Week 48 of the core study period and extension Week 24) are increasing in both treatment groups of Study CT-P10 1.1.

The sponsor also acknowledges that the actual baseline mean mTSS values recorded in Study CT-P10 1.1 are historically larger than other published data (including the pivotal REFLEX Study for MabThera registration in rheumatoid arthritis), but contends that these values cannot be directly compared because of the different x-ray scoring methods that have been applied. In rheumatoid arthritis studies, the two most commonly used methods of x-ray scoring to assess joint damage progression are the van der Heijde-modified Sharp method and Genant-modified Sharp scoring method. The sponsor reports that for many years both scoring methods have been accepted by regulatory agencies as valid tools. The x-ray data reported from the REFLEX Study for MabThera used the Genant-modified Sharp scoring method, whereas most other rheumatoid arthritis trials examining structural x-ray modification over time with treatment have used the van der Heijde-modified Sharp scoring method. Study CT-P10 1.1 calculated the mTSS values using the van der Heijde method. In the extended response, the sponsor has provided a published report[19] which indicates that because of the different arbitrary units used by each x-ray scoring method, raw van der Heijde–Sharp scores are numerically larger than raw Genant–Sharp scores by an approximate two-fold factor.

Evaluator comment (follow-up):

The additional explanation and data analysis provided by the sponsor during the course of the second round clinical evaluation provides a clearer picture of the x-ray dataset recorded in Study CT-P10 1.1 and its interpretation. Firstly, the observed x-ray data in a very small number of evaluable subjects in Study CT-P10 1.1 displays similar and expected mean progression at both time points, regardless of which rituximab treatment was administered (CT-P10 or MabThera). Furthermore, the sponsor has satisfactorily

[19] Peterfy CG, et al. Comparison of the Genant-modified Sharp and van der Heijde-modified Sharp scoring methods for radiographic assessment in rheumatoid arthritis. International *Journal of Clinical Rheumatology* 2011: 15-24.

explained the context of the historically high baseline mTSS values recorded in Study CT-P101 1.1 with reference to other biologic DMARD trials in rheumatoid arthritis, as well as the main comparator study (REFLEX).

Overall, the small volume of x-ray data reported in Study CT-P10 1.1 does not raise any significant efficacy concerns for a differential radiographic slowing effect between CT-P10 and MabThera in patients with rheumatoid arthritis, but the dataset has significant methodological limitations including a lack of statistical power and less than 50% of potentially evaluable subjects having actual recorded data at baseline and the relevant follow-up time point. The application of a linear extrapolation method to handle missing x-ray data may have assisted in the overall quantity of the x-ray data available for assessment.

Safety

Question 3

Could the sponsor comment on the potential reason(s) for the apparent increased incidence of acute infusion related reactions and neutropenia consistently observed with CT-P10 versus reference rituximab therapy across the CT-P10 clinical trial program?

Sponsor response:

In the response, the sponsor states that the overall incidences of infusion related reaction were similar between the treatment groups throughout all CT-P10 clinical trials except for the rheumatoid arthritis Study CT-P10 3.2. Table 15 provides a summary of the infusion related reaction data in the CT-P10 trial program.

Table 15: Summary of infusion related reactions in CT-P10 clinical trials (Safety Population)

	Study CT-P10 3.2 (Main Study Period)			Study CT-P10 1.1		Study CT-P10 1.3		Study CT-P10 3.3	
	CT-P10 (N=161)	Rituxan® (N=151)	MabThera® (N=60)	CT-P10 (N=102)	MabThera® (N=51)	CT-P10 maintenance (N=38)	Switched from MabThera® (N=20)	CT-P10 (N=70)	Rituxan® (N=70)
No. of Events	**39**	**15**	**15**	**27**	**15**	**1**	**1**	**22**	**21**
No. (%) of patients with ≥ 1 IRR	**33 (20.5)**	**12 (7.9)**	**13 (21.7)**	**20 (19.6)**	**10 (19.6)**	**1 (2.6)**	**1 (5.0)**	**16 (22.9)**	**17 (24.3)**
Related	**33 (20.5)**	**12 (7.9)**	**13 (21.7)**	**20 (19.6)**	**10 (19.6)**	**1 (2.6)**	**1 (5.0)**	**15 (21.4)**	**17 (24.3)**
Grade 1	16 (9.9)	3 (2.0)	6 (10.0)	11 (10.8)	4 (7.8)	1 (2.6)	0	4 (5.7)	6 (8.6)
Grade 2	15 (9.3)	9 (6.0)	7 (11.7)	8 (7.8)	6 (11.8)	0	1 (5.0)	9 (12.9)	11 (15.7)
Grade 3	2 (1.2)	0	0	1 (1.0)	0	0	0	2 (2.9)	0
Unrelated	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (1.4)**	**1 (1.4)**
No. (%) of patients with ≥ 1 serious IRR	0	0	0	1 (1.0)	0	0	0	1 (1.4)	0
No. (%) of patients with ≥ 1 IRR leading to discontinuation	2 (1.2)	3 (2.0)	1 (1.7)	2 (2.0)	0	0	0	1 (1.4)	0
Number (%) of patients with ≥ 1 IRR requiring any treatment	15 (9.3)	7 (4.6)	6 (10.0)	10 (9.8)	6 (11.8)	0	1 (5.0)	13 (18.6)	16 (22.9)

In the rheumatoid arthritis Study CT-P10 1.1, the proportion of patients experiencing infusion related reaction was identical in the two treatment groups (19.6% in each group; 20 of 102 in the CT-P10 arm and 10 of 51 in the MabThera arm). In the rheumatoid arthritis extension Study CT-P10 1.3, 1 patient in each treatment group recorded an infusion related reaction (2.6% (1 of 38) in the CT-P10 maintenance group and 5.0% (1 of 20) in the CT-P10 switch cohort). In the follicular lymphoma Study CT-P10 3.3, 22.9% (16 of 70) of subjects in the CT-P10 group 24.3% (17 of 70) of patients in the Rituxan arm experienced infusion related reaction.

During the main study period of Study CT-P10 3.2 (that is, up to Week 48), a lower proportion of patients in the Rituxan group experienced at least 1 infusion related reaction (7.9%; 12 of 151) compared to the two other treatment arms (20.5% (33 of 161) in the CT-P10 group and 21.7% (13 of 60) in the MabThera arm). The sponsor states that the

incidence rates of infusion related reaction in the Study CT-P10 3.2 are consistent with the frequency of acute infusion related reaction reported in rheumatoid arthritis patients who were pre-treated with IV corticosteroid in historical studies with rituximab. In the DANCER study (WA17043), medically-reviewed acute infusion related reaction following the first infusion of rituximab in the first treatment course occurred in 18 of 65 (28%) patients who received 1000 mg of rituximab without IV corticosteroid premedication compared to 24 of 127 (19%) of subjects who received rituximab with IV corticosteroid premedication.

In addition, the CT-P10 trials showed no notable differences among the treatment groups with regard to the seriousness, severity and clinical characteristics of the infusion related reactions. All infusion related reaction events in Study CT-P10 3.2 were graded as either mild (grade 1) or moderate (grade 2), with the exception of 2 patients in the CT-P10 group who experienced severe (grade 3) AEs. All patients who experienced infusion related reaction recovered without sequelae.

The sponsor states that the proportion of patients who experienced treatment emergent neutropenia were similar between the treatment groups in CT-P10 rheumatoid arthritis studies. Table 16 provides a summary of the of the neutropenia data (search conducted using several MedDRA preferred terms) in the CT-P10 clinical trial program.

Table 16: Summary of neutropenia events in CT-P10 clinical trials (Safety Population)

No. (%) of patients with ≥ 1 event (PT)	Study CT-P10 3.2 (Main Study Period)			Study CT-P10 1.1		Study CT-P10 1.3		Study CT-P10 3.3	
	CT-P10 (N=161)	Rituxan* (N=151)	MabThera* (N=60)	CT-P10 (N=102)	MabThera* (N=51)	CT-P10 maintenance (N=38)	Switched from MabThera* (N=20)	CT-P10 (N=70)	Rituxan* (N=70)
Neutropenia	1 (0.6)	3 (2.0)	1 (1.7)	2 (2.0)	2 (3.9)	0	0	24 (34.3)	16 (22.9)
Autoimmune neutropenia	0	0	0	0	0	0	0	0	0
Cyclic neutropenia	0	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	2 (2.9)	2 (2.9)
Idiopathic neutropenia	0	0	0	0	0	0	0	0	0
Leukopenia	3 (1.9)	1 (0.7)	1 (1.7)	1 (1.0)	0	0	0	1 (1.4)	2 (2.9)
Neutropenia neonatal	0	0	0	0	0	0	0	0	0
Neutrophil count decreased	3 (1.9)	0	0	0	0	0	0	0	0
White blood cell count decreased	0	0	0	0	0	0	0	0	1 (1.4)

PT: Preferred Terms

During the main study period of Study CT-P10 3.2, 0.6% (1 of 161) of patients in the CT-P10 group, 2.0% (3 of 151) of subjects in the Rituxan arm and 1.7% (1 of 60) of patients in the MabThera group recorded neutropenia. However in the same trial, another 3 CT-P10 subjects (1.9%) recorded "neutrophil count decreased" versus no such cases in the other two groups. In Study CT-P10 1.1, 2 patients in each treatment group (CT-P10 and MabThera) recorded neutropenia, and no subjects experienced neutropenia in Study CT-P10 1.3.

In the follicular lymphoma Study CT-P10 3.3, the number and proportion of patients who experienced neutropenia was higher in the CT-P10 group (34.3% (24 of 70) versus 22.9% (16 of 70) of patients in the Rituxan group). However, the sponsor explains this difference by more patients in the CT-P10 treatment group having bone marrow involvement at baseline (45 (64.3%) patients in the CT-P10 group versus 33 (47.1%) subjects in the Rituxan arm). Among the patients who recorded neutropenia, 18 of 24 (75%) patients in the CT-P10 group and 7 of 16 (43.8%) subjects in the Rituxan arm had bone marrow involvement at baseline. Published data indicates that patients with bone marrow involvement have significantly lower neutrophil counts both at diagnosis and following chemotherapy. Regarding severity, there was no notable difference between the two treatment groups of Study CT-P10 3.3 for greater than grade 3 neutropenia: 20 (16.9%) patients in the CT-P10 group and 13 (12.9%) subjects in the Rituxan arm.

Evaluator comment:

The sponsor has provided a summary of the risk of acute infusion related reactions with CT-P10, which shows a similar incidence and severity of these events with reference rituximab formulations in all of the trials except the main study period of Study CT-P10 3.2. The higher incidence of infusion related reactions up to Week 48 with CT-P10 (20.5%) versus reference products (11.8% MabThera and Rituxan data combined; 21.7% with MabThera) was driven by an unexpectedly low rate of infusion related reaction observed with Rituxan (7.9%), which was inconsistently low according to published historical data for rituximab (expected to be ~ 20%). The result of Study CT-P10 3.2 (that is, low rate of infusion related reaction with Rituxan) is probably best explained as a chance finding confined to Study CT-P10 3.2 and has not been replicated in any other rituximab trial.

In the CT-P10 rheumatoid arthritis studies, the incidence and severity of neutropenia was comparable and within expectations for all three rituximab formulations. In the advanced follicular lymphoma Study CT-P10 3.3, the percentage of subjects who recorded treatment emergent neutropenia with CT-P10 (34.3%; 24 of 70) was higher than that observed in the Rituxan arm (22.9%; 16 of 70). In the S31 response, the sponsor has a provided a clear and valid explanation of this finding as being related to a higher incidence of bone marrow involvement at baseline in the CT-P10 group (64.3% versus 47.1% in the Rituxan arm). Consistent with the medical literature, subjects with bone marrow disease in Study CT-P10 3.3 were over-represented in the occurrence of neutropenia during the trial. Among the patients reported to experience neutropenia in Study CT-P10 3.3, 18 of 24 (75%) subjects in the CT-P10 group and 7 of 16 (43.8%) patients in the Rituxan arm had bone marrow disease at baseline.

Second round benefit-risk assessment

After consideration of the responses to the clinical questions, the potential benefits of CT-P10 in the proposed usage are consistent with those detailed in the First round assessment. In particular, the sponsor has provided further analyses (post-hoc) about the reasons for a higher rate of re-treatment with CT-P10 versus MabThera in the initial rheumatoid arthritis trial (Study CT-P10 1.1). This was found to be consequential to the protocol determined allowance for investigator led re-treatment and was not driven by a lack of comparative efficacy. In addition, none of the CT-P10 studies showed a trend for earlier B-cell count recovery between the three different rituximab formulations that have been studied. Furthermore, there was no impact upon efficacy outcomes in any of the CT-P10 trials (rheumatoid arthritis and follicular lymphoma).

Interpretation of the full tabulated x-ray data obtained in Study CT-P10 1.1 shows that CT-P10 exhibits comparable efficacy to MabThera in slowing the rate of structural disease progression over 48 weeks in the core study period and at Week 24 of the extension study phase. During the second round clinical evaluation process, the applicant provided additional commentary and analysis of the radiographic dataset (upon request) to support that the observations were scientifically valid. Overall, the x-ray data is sufficient for CT-P10 to support the registration claim of radiographic benefit as an add-on sub-claim to the overall rheumatoid arthritis treatment indication.

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of CT-P10 are unchanged from those identified in the First round assessment of this report. In their response the sponsor has provided a clear and acceptable reason for the observed higher rate of infusion related reaction with CT-P10 versus reference rituximab in the main study

period of Study CT-P10 3.2, as well as a valid rationale for the higher frequency of neutropenia with CT-P10 versus Rituxan therapy in Study CT-P10 3.3. Overall, the safety dataset with CT-P10 does not raise any new or unexpected safety concerns with CT-P10 and the pharmacovigilance strategies proposed by the applicant meet the minimum standards for consideration of registration. The increased rate of serious and opportunistic infection with rituximab versus placebo; as well as the higher incidence of permanent treatment discontinuation due to AEs and neutropenia remain a consistent safety signal, which is comparable between the three rituximab formulations (CT-P10, Rituxan and MabThera).

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed in the First Round assessment of this report. On the basis of biosimilarity, the overall benefit-risk balance of CT-P10 treatment in the four proposed treatment indications is favourable. Clinically relevant efficacy with acceptable toxicity has been directly observed with CT-P10 therapy in the third line rheumatoid arthritis treatment population, as well in subjects with advanced follicular lymphoma (Study CT-P10 3.3). The results of all the CT-P10 trials have validity to contemporary Australian practice and internationally accepted rheumatoid arthritis and lymphoma treatment guidelines. The major risks with CT-P10 therapy (versus placebo) are similar to the reference drug (MabThera), and include an increased risk of serious infection, infusion related reactions and neutropenia.

Second round recommendation regarding authorisation

Acceptance is recommended for the sponsor's proposed registration of CT-P10 to include the treatment of active rheumatoid arthritis, NHL, CLL and ANCA associated systemic vasculitis. The submission provides evidence that CT-P10 is therapeutically equivalent to MabThera in improving the signs and symptoms of active rheumatoid arthritis that are inadequately responding to methotrexate and been previously treated with anti-TNF drugs. This target treatment population is consistent with the approved rheumatoid arthritis treatment population for MabThera. In addition, CT-P10 shows comparable short term efficacy to Rituxan in adult patients with advanced follicular lymphoma. In terms of safety, the three formulations of rituximab appear to be clinically equivalent for the incidence and type of clinically significant safety concerns. The CT-P10 clinical study program shows an expected incidence of acute infusion related reactions, which were mostly mild or moderate in severity; and comparable rates of immunogenicity in rheumatoid arthritis and advanced follicular lymphoma patients. Moreover, the safety profile (incidence and type) of CT-P10 is within historical expectations for MabThera therapy in the two main target populations (rheumatoid arthritis as a model of autoimmune disease and advanced follicular lymphoma as the haematological malignancy model).

Approval of the sponsor's proposed registration for CT-P10 is recommended subject to:

- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study reports for the two on-going Phase III studies (CT-P10 3.2 and 3.3) as well as the interim and final data for Study CT-P10 3.4 (proposed Phase III trial in patients with low tumour burden follicular lymphoma).

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[20]

Truxima/Ritemvia is proposed for the same indications approved for the reference product MabThera (Roche Products Pty Ltd): to be used for the treatment of Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukaemia (CLL), Rheumatoid Arthritis (RA), or granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Administration of Truxima/Ritemvia involves intravenous infusion at varying dose regimens dependent upon the condition being treated.

- The sponsor has submitted EU-RMP version 4.0 (date 15 December 2016; Data Lock Point (DLP) 4 May 2016) and ASA version 1.0 (date February 2017) in support of this application.
- Along with the responses, the sponsor provided updated EU RMP version 7.0 (date 18 May 2017; DLP 26 October 2016) and ASA version 2.0 (date October 2017).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies as proposed in the EU RMP version 7.0 (date 18 May 2017; DLP 26 October 2016) are summarised below in Table 17.

Table 17: Risk Management plan

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Acute infusion-related reactions	ü	ü	ü	ü
	Infections including serious infections	ü	ü	ü	ü
	Impaired immunisation response	ü	–	ü	–
	Progressive multifocal leukoencephalopathy (PML)	ü	ü	ü	ü
	Neutropenia (incl. prolonged)	ü	–	ü	–
	HBV reactivation	ü	ü	ü	–

[20] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Tumour lysis*	ü	–	ü	–
	Gastrointestinal perforation*	ü	–	ü	–
	Hypogammaglobulinaemia**/***	ü	–	ü	–
	Stevens-Johnson syndrome/Toxic epidermal necrolysis	ü	–	ü	–
Important potential risks	Posterior reversible encephalopathy syndrome (PRES)*	ü	ü	ü	–
	Malignancy**/***	ü	ü	ü	–
	Impact on cardiovascular disease**/***	ü	–	ü	–
	Prolonged B-cell depletion	ü	–	ü	–
	Increased grade 3 or 4 and serious blood and lymphatic system adverse events in patients >70 years*	ü	–	ü	–
	Acute myeloid leukaemia/myelodysplastic syndrome*	ü	–	ü	–
	Second primary malignancy*	ü	ü	ü	–
	Off-label use in autoimmune disease**/***	ü	–	ü	–
	Off-label use in paediatric patients	ü	ü	ü	–
	Relapse of GPA/MPA***	ü	–	ü	–
	Administration route error*	ü	–	ü	ü
Missing information	Use during pregnancy or lactation	ü	–	ü	–
	Immunogenicity and autoimmune disease**/***	ü	ü	ü	–
	Long-term use in GPA/MPA patients***	ü	–	ü	–

*NHL/CHL indication; **rheumatoid arthritis indication; ***GPA/MPA indication

Routine pharmacovigilance is proposed for all safety concerns and missing information. Additional pharmacovigilance is proposed for the specified safety concerns and missing information as indicated in the table above, and consists of:

- three clinical studies (CT-P10 3.2, CT-P10 3.3, CT-P10 3.4), and
- targeted follow-up questionnaires.

While there is no Australian involvement in the clinical studies, the sponsor has advised them to be relevant to the Australian population.

Routine risk minimisation is proposed for all safety concerns and missing information. Additional risk minimisation is proposed to address specified safety concerns (see Table 17 above), and consists of healthcare professional and patient educational materials and a Patient Alert Card (PAC).

New and outstanding recommendations from second round evaluation

The sponsor has satisfactorily addressed the recommendations made by the RMP evaluator.

The sponsor's commitment to update the RMP/ ASA to incorporate results of the ongoing studies is noted.

The sponsor has confirmed that the educational material and Patient Alert Card mock-ups provided with the EU RMP will be adapted for use in Australia. Draft additional risk minimisation materials adapted for Australia should be provided to the TGA for review when available. Regarding the HCP educational material, the sponsor should describe to whom and how many copies are proposed to be distributed.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is: Implement EU RMP version 7.0 (date 18 May 2017; DLP 26 October 2016) and ASA version 2.0 (date October 2017), and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

This submission is to register a new biosimilar medicine; rituximab 500 mg in 50 mL and 100 mg in10 mL concentrate for solution for intravenous infusion. This product is also known as CT-P10. The sponsor proposes two trade names, Truxima and Ritemvia. Both of these trade names are approved in the EU. For the purpose of this overview, Truxima will be used when referencing the trade name.

The submission is based on similarity to the approved product MabThera (100 mg vial AUST R 60318 and 500 mg vial AUST R 60319), sponsored in Australia by Roche Products Pty Ltd. The sponsor proposes the same indications and dosing as MabThera. MabThera was first included on the ARTG in October 1998. MabThera is a formulation for IV

administration only. MabThera SC is a different formulation for subcutaneous administration. This submission does not include a subcutaneous formulation.

Rituximab is a chimeric murine/human immunoglobulin (IgG1) monoclonal antibody containing murine light and heavy chain variable region sequences (Fab domain) and human constant region sequences (Fc domain) that bind with high affinity and specificity to the CD20 antigen found on the surface of normal and malignant B-cells in humans. The proposed therapeutic mechanism of action of rituximab is to promote B-cell lysis via complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis.

Truxima was approved in the EU on 21 February 2017 for NHL, CLL, rheumatoid arthritis and GPA/MPA indications. It was also approved in South Korea on 16 November 2016 and Georgia on 7 July 2017 for these indications. Applications based on these indications were submitted to USA on 28 April 2017, Canada on 21 July 2017, Singapore on 16 June 2017 and Switzerland on 27 February 2017 and remain under evaluation. Applications are also under evaluation in numerous other countries. None of these submissions have been withdrawn due to safety or efficacy concerns.

The development program for CT-P10 rituximab followed EU guidelines for demonstration of biosimilarity. The program followed a step-wise approach to demonstrating comparability with MabThera, involving physicochemical comparability data, non-clinical comparability data and clinical comparability data. Pre-submission guidance was sought from TGA regarding comparability testing. Bridging studies were performed to demonstrate equivalence between EU-sourced MabThera used in clinical trials and the Australian reference product. Relevant guidelines for assessment of biosimilars are detailed in the TGA reference document, *Regulation of biosimilar medicines*, v2.0, December 2015.

Relevant guidance for this submission included:

- CHMP/437/04 Rev1 Guideline on similar biological medicinal products. EMA/CHPM/BWP247713/2012 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1).
- EMEA/CHMP/BMWP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues. This guideline also assists with extrapolation of indications for biosimilars.
- EMA/CHMP/BMWP/86289/2010 Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.
- EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues.
- CPMP/EWP/556/95 rev 1/Final points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis
- EMA/CHMP/205/95/Rev.4 Guideline on the evaluation of anticancer medicinal products in man (and relevant appendices).

Quality

The evaluator concluded that there are no objections to the approval of Truxima on quality grounds, other than Good Manufacturing Practice (GMP) clearance for three

manufacturing processes. The sponsor had expected these GMP issues to be resolved but they remain under evaluation.[21]

During the development program for Truxima, EU-sourced MabThera and US-sourced Rituxan were used as reference products to demonstrate biosimilarity. Comprehensive 3-way comparability testing was submitted which demonstrates comparability of CT-P10, MabThera and Rituxan in terms of primary structure, higher order structure, purity, fragmentation, charge variants, glycosylation variants and biological activity. Some differences were noted in terms of terminal glutamine modifications, which were small and the sponsor provided justification, including data from the literature and from the comparability studies, to indicate these are unlikely to cause differences between CT-P10 and the comparators. Other subtle changes in fragments, charged species and glycans were seen but the sponsor provided functional data to suggest these will have little impact. The evaluator considers that the sponsor has provided adequate data to support the conclusion of similarity between CT-P10, MabThera and Rituxan.

Additional bridging comparability data were submitted comparing EU-sourced and Australian-sourced MabThera. These data were considered to satisfactorily establish similarity between EU-sourced MabThera and the Australian reference product.

The evaluator considers that the sponsor has demonstrated that Truxima is comparable to MabThera in terms of structure, species, function and degradation profile. There are no objections to the registration of Truxima from sterility, endotoxin, container safety and viral safety assessments. The proposed PI, CMI and labels are acceptable from a quality perspective.

Nonclinical

The nonclinical evaluator concluded that there are no nonclinical objections to the registration of Truxima provided EU-sourced MabThera is accepted to be identical or highly comparable to Australian MabThera. This has been confirmed so there are no outstanding nonclinical issues.

The scope of the nonclinical program is considered adequate based on the TGA-adopted EMA guideline. The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat-dose toxicity. The nonclinical studies were conducted using EU-sourced MabThera as the reference product. No meaningful differences between Truxima and MabThera were observed in the comparative pharmacology, pharmacokinetic and toxicity studies.

The sponsor has proposed Pregnancy Category C.[3] This matches the existing category for MabThera and is considered appropriate.

Clinical

The clinical evaluator recommends approval of Truxima for the proposed indications based on the clinical evidence provided in this submission.

The clinical dossier included the following data:

- one pivotal clinical pharmacology study (Part 1 of Study CT-P10 3.2) in rheumatoid arthritis patients that aimed to demonstrate 3-way pharmacokinetics equivalence between CT-P10, MabThera and Rituxan.

[21] The GMP issues were resolved prior to registration.

- supporting pharmacokinetics equivalence data between CT-P10 and Rituxan was examined in Part 1 of Study CT-P10 3.3 (advanced follicular lymphoma patients) and between CT-P10 and MabThera in Study CT-P10 1.1 (rheumatoid arthritis patients).
- one pivotal Phase III, efficacy/safety study (CT-P10 3.2) in patients with active rheumatoid arthritis. Clinical and pharmacokinetics data up to Week 48 was provided in this submission.
- one pivotal Phase I/III, efficacy/safety study (CT-P10 3.3) in patients with advanced follicular lymphoma. Clinical data up to Week 24 was provided.
- one supporting open label, maintenance treatment trial in subjects with rheumatoid arthritis (Study CT-P10 1.3) that provided clinical and pharmacodynamic data for up to 24 weeks in the extension phase.
- one supporting open label, single-arm, pilot Phase I trial of CT-P10 in patients (with only 1 subject enrolled) with relapsed or refractory DLBCL.

All of the clinical studies provided in this submission were conducted in accordance with the principles of Good Clinical Practice (GCP). There were two GCP non-compliant sites (1 in Study CT-P10 3.2 and 1 in Study CT-P10 3.3) identified by the contract research organisation, which were closed due to scientific misconduct and serious GCP non-compliance. The patients enrolled at these sites were excluded from all analysis populations, but included in sensitivity analyses for the primary pharmacokinetics endpoint of Study CT-P10 3.3 and serious adverse events (SAEs) of Study CT-P10 3.2. The exclusion of data from these sites is not considered to compromise the overall datasets.

Pharmacokinetics

The submission presented three studies to demonstrate similarity in pharmacokinetics characteristics between CT-P10 and rituximab (EU-sourced MabThera and US-sourced Rituxan), two in patients with rheumatoid arthritis and one in patients with advanced follicular lymphoma.

Study CT-P10 1.1

The Phase I Study CT-P10 1.1 in adult patients with rheumatoid arthritis had the primary objective of demonstrating the pharmacokinetics equivalence of CT-P10 and MabThera up to Week 24. For the pharmacokinetics population, the ratios (with 90% CIs) of the geometric means (CT-P10 to MabThera) were 96.90% (88.10 to 106.58) for $AUC_{0\text{-last}}$ and 95.77% (89.40 to 102.60) for C_{max}. These results fell within the pre-determined equivalence margin of 80% to 125%, demonstrating pharmacokinetics equivalence between CT-P10 and MabThera. This study also demonstrated similarity with MabThera for a range of secondary pharmacokinetics endpoints including T_{max}, $T_{1/2}$, AUC over several time frames, drug clearance (CL) apparent volume of distribution (Vd) and volume of distribution at steady state (Vss).

Part 1 of the 3-arm Phase III Study CT-P10 3.2 in subjects with rheumatoid arthritis had pharmacokinetics endpoints as a co-primary objective, aiming to demonstrate 3-way pharmacokinetics equivalence of CT-P10, MabThera and Rituxan for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} over the first 24 weeks. 189 patients were randomly assigned to study drug: 64 to CT-P10, 65 to Rituxan and 60 to MabThera. The 90% CIs of ratio of geometric means for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were completely contained within the pre-specified equivalence range of 80% to 125%, demonstrating pharmacokinetics equivalence of CT-P10, MabThera and Rituxan (Table 18).

Table 18: Primary pharmacokinetics results for Part 1 of Study CT-P10 3.2 (pharmacokinetics Population; Up to Week 24)

Parameter	Comparison	Treatment	N	Geometric LS Mean[1]	Ratio (%) of Geometric LS Means[1]	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		
$AUC_{0\text{-}tau}$ (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		

Study CT-P10 3.3

Study CT-P10 3.3 was a Phase III trial in subjects with advanced follicular lymphoma and had a co-primary objective of demonstrating the pharmacokinetics equivalence of CT-P10 with Rituxan at Cycle 4 (Weeks 9 to12) of the core study period. For the pharmacokinetics population, the ratios (with 90% CIs) of the geometric means (CT-P10 to Rituxan) were 95.31% (81.01 to 112.13) for AUC_{tau} and 101.38% (93.49 to 109.94) for C_{max}, entirely within the equivalence range of 80% to 125% indicating equivalent pharmacokinetics for CT-P10 and Rituxan in patients with advanced follicular lymphoma.

Analyses of the impact of anti-drug antibodies on pharmacokinetics were performed for CT-P10 1.1 and CT-P10 3.2. These concluded that anti-drug antibodies presence resulted in reduced drug exposure but the impact was similar between CT-P10, MabThera and Rituxan.

The clinical evaluator concluded that the studies have adequately demonstrated pharmacokinetics equivalence for CT-P10 with MabThera and Rituxan.

Pharmacodynamics

The submission presented four studies to demonstrate similarity in pharmacodynamic characteristics between CT-P10, MabThera and Rituxan. B-cell counts were the key pharmacodynamic endpoint, but it is noted that there is not a strong correlation between the extent of B-cell reduction and the magnitude of the clinical efficacy response in rheumatoid arthritis and NHL.

Study CT-P10 1.1

The Phase I Study CT-P10 1.1 in adult patients with rheumatoid arthritis had a secondary objective of examining the pharmacodynamic effects of CT-P10 compared to MabThera for up to 72 weeks of treatment follow-up. Study CT-P10 1.3 was an open label, single-arm extension of CT-P10 1.1 in which the long term safety (including B-cell kinetics) of CT-P10 was investigated (up to 2 years). Subjects could receive up to 4 courses of rituximab in total, though most received 2 or 3 treatment courses across the studies.

Earlier B-cell recovery was noted in the CT-P10 arm of Study CT-P10 1.1 (see Table 3, above), raising the possibility of a difference in duration of action, particularly when considered in the context of a higher rate of re-treatment with CT-P10 (52.9% in the CT-P10 arm versus 43.1% in the MabThera group).

In response to clinical questions, the sponsor explained that the higher rate of re-treatment with CT-P10 versus MabThera observed in Study CT-P10 1.1 was a consequence of investigator discretion (as per the trial protocol) and other factors including adverse events and consent withdrawal in a small study population, rather than being reflective of any significant clinical difference between CT-P10 and MabThera. The proportion of subjects eligible for re-treatment in Study CT-P10 1.1 was identical (64.7%) between the two treatment groups. The study remained blinded when re-treatment decisions were made by investigators, addressing the risk of bias in re-treatment decisions. Analysis of time to eligibility for re-treatment was similar between both groups. The sponsor's response also contained data showing that B-cell recovery kinetics in the rheumatoid arthritis studies (CT-P10 1.1 and the larger Study CT-P10 3.2) were similar between CT-P10 and reference products, as well as being consistent with published historical data.

Study CT-P10 1.3

In Study CT-P10 1.3, the extent and duration of B-cell responses were similar between the CT-P10 maintenance and switch groups.

Study CT-P10 3.2

The Phase III Study CT-P10 3.2 in subjects with rheumatoid arthritis collected pharmacodynamic data up to Week 48 as a pre-specified secondary objective. This study was designed with re-treatment at Weeks 24 and 26. B-cell counts decreased to below the LLOQ (20 cells/μL) immediately after the first infusion for all patients except 1 in the CT-P10 group, and then remained below this level up to Week 24 in the majority of patients (around 96%) in all treatment groups. Early B-cell recovery was infrequent after the second course of treatment for all products.

Study CT-P10 3.3

Study CT-P10 3.3 in patients with advanced follicular lymphoma had a secondary objective of evaluating the B-cell kinetics of CT-P10 and Rituxan up to core Cycle 8 of therapy (24 weeks). B-cell depletion was similar in both treatment arms.

The clinical evaluator concluded that pharmacodynamic equivalence of CT-P10 to MabThera has been adequately demonstrated.

Efficacy

The submission contains two pivotal Phase III trials: Study CT-P10 3.2 in adult patients with active rheumatoid arthritis and Study CT-P10 3.3 in subjects with advanced follicular lymphoma. Supportive efficacy studies include the Phase I Study CT-P10 1.1 in patients with active rheumatoid arthritis and its open label, extension Study CT-P10 1.3.

The comparator product used in Studies CT-P10 1.1 and CT-P10 1.3 was MabThera. Both MabThera and Rituxan were used in Study CT-P10 3.2 to establish a robust scientific bridge between the three products in terms of pharmacokinetics. Given the evidence of structural and functional similarity between CT-P10, MabThera and Rituxan as well as 3-way pharmacokinetics equivalence demonstrated in Part 1 of Study CT-P10 3.2, Rituxan was used as a comparator in Part 2 of Study CT-P10 3.2 as well as in Study CT-P10 3.3.

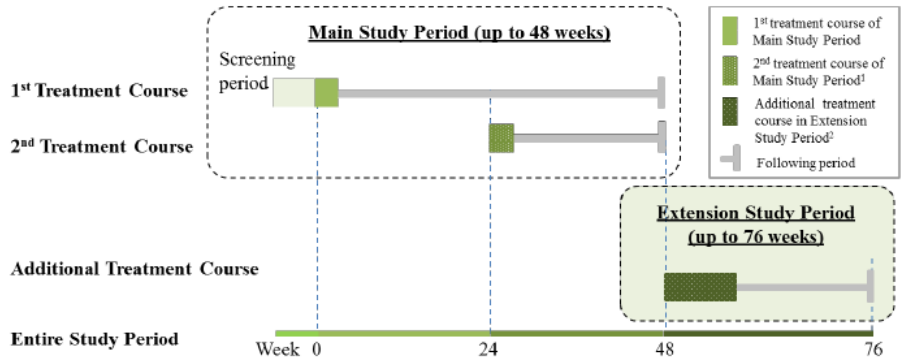
This approach was discussed with CHMP/SAWP;[22] during the Scientific Advice procedure and was considered acceptable.

Study CT-P10 3.2

Study CT-P10 3.2 was a randomised, double blind, parallel group (three arms), Phase III comparative equivalence trial in adult patients with moderately to severely active rheumatoid arthritis who had a history of inadequate response to anti-TNF drugs and who were receiving methotrexate 7.5 to 25 mg/week at baseline. Part 1 was designed to demonstrate 3-way pharmacokinetics equivalence between CT-P10, MabThera and Rituxan during the first treatment course. Part 2 was designed to demonstrate therapeutic equivalence between CT-P10 and MabThera/Rituxan based on DAS28-CRP at Week 24. The study consisted of a main treatment period of 48 weeks followed by an extension treatment phase of 24 weeks, though this submission only contained data for the main study period (up to Week 48).

372 patients were randomly assigned to treatment. The treatment cohorts were well balanced for demographic characteristics, baseline disease characteristics and mean weekly methotrexate dose (14.61mg for CT-P10, 15.01mg for MabThera/Rituxan). Patients received up to 4 infusions of study drug over 2 treatment courses during the main study period, in combination with methotrexate and folic acid. Each treatment course consisted of 2 infusions of study drug (1000 mg of CT-P10, MabThera or Rituxan by IV infusion) with a 2-week interval between the first and second infusions.

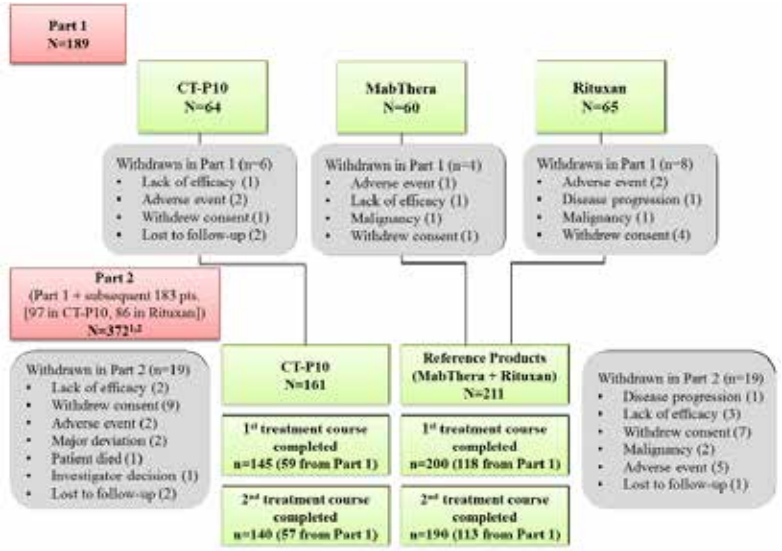
Figure 3: Study CT-P10 3.2 schematic



[1] For patients who met the pre-defined safety criteria for additional treatment course, additional 2 infusions were administered on Week 24 and Week 48 (2nd treatment course in the Main Study Period).
[2] Patients who completed all scheduled visit up to Week 48, regardless of the number of treatment courses they are treated during the Main Study Period, and met the pre-defined safety criteria could receive an additional treatment course during the Extension Study Period (2 infusions at Extension Week 0 and Week 2). Extension Study Period could be initiated between Week 48 and Week 52 of the Entire Study Period based on the results assessed within 8 weeks from Extension Week 0.

[22] CHMP/SAWP Committee on Medicinal Products for Human Use (EMA)/ Scientific Advice Working Party

Figure 4: Participant flow up to Week 48 in Study CT-P10 3.2 (Main study period)



CT-P10 and the reference drugs (MabThera and Rituxan) demonstrated equivalent outcomes for the primary efficacy endpoint of the mean change from baseline to Week 24 in the DAS28-CRP score (Table 19). The estimated treatment difference was -0.05 and the 95% CI (-0.29 to 0.20) was fully contained within the predefined equivalence margin of -0.6 to +0.6, thereby supporting therapeutic equivalence of CT-P10 to the reference products. Outcomes for secondary endpoints, including ACR20, ACR50 and ACR70 responses at Week 24, were supportive of equivalent efficacy. Between Weeks 24 and 48, patients (most of whom were re-treated with a second course of rituximab) demonstrated maintenance of treatment response.

Table 19: Analysis of DAS28 (ANCOVA) in Study CT-P10 3.2 (Part 2): All randomised population and efficacy population

Visit/ Treatment Group	N'	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
All-Randomised Population				
DAS28 (CRP) at Week 24				
CT-P10	140	-2.13 (0.175)	-0.05	(-0.29, 0.20)
MabThera + Rituxan	197	-2.09 (0.176)		
DAS28 (ESR) at Week 24				
CT-P10	141	-2.41 (0.181)	-0.06	(-0.31, 0.20)
MabThera + Rituxan	197	-2.36 (0.181)		
Efficacy Population				
DAS28 (CRP) at Week 24				
CT-P10	139	-2.14 (0.177)	-0.05	(-0.29, 0.20)
MabThera + Rituxan	196	-2.09 (0.176)		
DAS28 (ESR) at Week 24				
CT-P10	140	-2.41 (0.182)	-0.06	(-0.31, 0.19)
MabThera + Rituxan	196	-2.35 (0.182)		

The clinical evaluator concluded that the efficacy data up to Week 48 in this study are sufficient to establish therapeutic equivalence between CT-P10 and reference rituximab products for the treatment of adult patients with rheumatoid arthritis. Study CT-P10 3.2 was overall well conducted, the design was consistent with the TGA guideline for

assessment of rheumatoid arthritis and the findings are applicable to the Australian context.

Study CT-P10 1.1 and Study CT-P10 1.3

Study CT-P10 1.1 and its open label extension Study CT-P10 1.3 provided supportive evidence of comparable efficacy of CT-P10 and MabThera for the treatment of rheumatoid arthritis. The proportion of patients achieving ACR20, ACR50 and ACR70 response up to Week 24 was similar in the CT-P10 and MabThera treatment groups. Efficacy data following 2 or 3 treatment courses in these studies (up to 104 weeks treatment follow-up) indicated that responses were maintained in those who continued to receive CT-P10 and were similar in those subjects who switched from MabThera to CT-P10 in the open label trial.

Radiographic data from Study CT-P10 1.1 was reviewed in the second round of evaluation. The additional explanation and data analysis supports the claim of comparable efficacy to MabThera in slowing the rate of structural disease progression. The analysis of radiographic data from this study was constrained by a lack of statistical power, but the evaluator concluded that the submission contains adequate evidence to support the claim of radiographic benefit as part of the rheumatoid arthritis indication.

Study CT-P10 3.3

Study CT-P10 3.3 was a Phase I and III, 2-part, randomised, parallel group, active controlled, double blind trial in adult patients with advanced follicular lymphoma. The primary objective of Part 1 was to demonstrate similarity in pharmacokinetics between CT-P10 and Rituxan and Part 2 was to demonstrate non-inferiority in efficacy, as determined by Overall Response Rate, of CT-P10 to Rituxan when co-administered with cyclophosphamide, vincristine and prednisone (CVP). The Overall Response Rate was defined as the proportion of responder patients who achieved complete response (CR) plus unconfirmed complete response (CRu) plus partial response (PR) over 8 cycles of treatment in the core study period of Study CT-P10 3.3. This Overall Response Rate definition was consistent with the 1999 IWG criteria in previously untreated patients with advanced (stage III or IV) CD20+ follicular lymphoma.

This study consisted of a screening period of up to 4 weeks with a core study period of up to 8 treatment cycles, followed by a maintenance study phase of up to 2 years and a follow-up treatment period (defined as until death, or 3 years from Day 1 of Cycle 1 of the core study period for the last patient).

Rituximab was dosed according to body surface area (375 mg/m^2) and administered on Day 1 of each treatment cycle. A maximum of 8 cycles were administered with each Cycle lasting 21 days.

140 patients were randomised, 70 to each treatment group. The population characteristics were evenly balanced between the groups. 8 subjects in each group discontinued study treatment before completion of the core study period.

The primary efficacy outcome for Part 2 of Study CT-P10 3.3 was non-inferiority of CT-P10 to Rituxan, as determined by overall response rate over 8 cycles of treatment in the core study period (24 weeks) as per the 1999 IWG criteria. The clinical evaluator concluded that overall response rate is an acceptable endpoint to demonstrate comparable efficacy in the advanced follicular lymphoma indication. The CHMP provided advice during the clinical development program that a non-inferiority study design for advanced follicular lymphoma patients would be adequate to confirm efficacy in an oncological population given that the pivotal demonstration of therapeutic equivalence will be performed in the more sensitive rheumatoid arthritis population. The pre-specified overall response rate non-inferiority margin of -7% is consistent with the EMA Guidance choice of non-inferiority margin. The primary efficacy outcome results are shown in Table 20. The

difference in Overall Response Rate for the per protocol and intention to treat population were both on the positive side of the pre-specified non-inferiority margin of -7%, confirming non-inferior efficacy in the oncological indication. The non-inferiority margin was based on absolute point estimate difference rather than 95% CI. The evaluator has advised that the lower bound of the 95% CI would lie within the 7% margin. The European Public Assessment Report (EPAR) references the 95% CI for the Overall Response Rate difference in the PP population: 4.3% (95%CI -4.14 to 13.33).

Bone marrow examination results and B-symptoms at Week 24 were similar between CT-P10 and Rituxan. Other efficacy endpoints assessed in Study CT-P10 3.3 (but not available in this submission) included the Overall Response Rate at 24 weeks as per the 2007 IWG criteria, tumour response assessment (based on serial imaging), serum lactate dehydrogenase (LDH) levels and various time to event parameters including progression free survival, response duration, disease free survival and overall survival. The final clinical study report is expected to be available in the fourth quarter of 2019.

Table 20: CT-P10 3.3 Results for the primary efficacy outcome

Population	CT-P10	Rituxan	Difference[1]
Overall Response	Number (%) of Patients		%
PP population	**n=66**	**n=68**	
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)	
Stable disease	1 (1.5)	2 (2.9)	
RD/PD	1 (1.5)	2 (2.9)	
Unable to assess[2]	0	1 (1.5)	
ITT population	**n=70**	**n=70**	
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)	
Stable disease	1 (1.4)	2 (2.9)	
RD/PD	1 (1.4)	2 (2.9)	
Unable to assess[2]	0	1 (1.4)	
Missing[3]	1 (1.4)	2 (2.9)	

Abbreviations: CR, complete response; CRu, unconfirmed complete response; ITT, intent-to-treat; PP, per-protocol; IWG, International Working Group; ORR, overall response rate; PR, partial response; RD/PD, relapsed disease/progressive disease.

1. Difference was calculated using percentages not the round off values.
2. Unable to assess category included a patient (Patient 1202-3005) who did not meet the minimum duration (8 weeks) for best overall response. The patient was evaluated as PR at EOT1 visit (after 49 days from randomization).
3. Missing cases included patietns who had no efficacy assessment results at post treatment visits (Patient 1203-3002 in CT-P10 treamtent group, Patients 2601-3002 and 2703-3001 in Rituxan treatment group)

Note: Overall response was based on the 1999 IWG criteria.

Study CT-P10 1.2

Study CT-P10 1.2, a Phase I, open label, single arm trial of CT-P10 in relapsed or refractory diffuse large B-cell lymphoma closed prematurely 2 months after enrolling its first and only subject. The reason for premature study closure was the low rate of subject enrolment related to stringent inclusion and exclusion criteria.

A synopsis for Study CT-P10 3.4, a Phase III randomised, parallel group, active controlled, double-blind trial designed to evaluate the comparative efficacy and safety of CT-P10 and Rituxan in subjects with low tumour burden follicular lymphoma, was included in the submission, but no patient data was provided as the trial was still recruiting subjects. The study results are expected in 2021.

Extrapolation to all approved MabThera indications

The sponsor provided a literature review and scientific justification to support the proposed extrapolation of treatment indications for CT-P10 to all MabThera indications. The Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) notes that '*extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibody (mAb), not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. Applicants should support such extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action.*'

The clinical evaluator concluded that extrapolation of all treatment indications approved for MabThera to CT-P10 is appropriate based on the evidence provided in this submission supporting the comparability of CT-P10 and MabThera with regard to mechanisms of action, pharmacokinetics, pharmacodynamics, efficacy and safety. The data submitted is in keeping with the TGA-adopted Guideline.[9]

Table 21: Number of patients who received at least 1 dose of study drugs in the CT-P10 studies

Study	Patient Population	CT-P10	MabThera	Rituxan	Total
	Overall Exposure – Number of Patients				
CT-P10 1.2(a pilot study)	DLBCL	1	-	-	1
CT-P10 1.1 Maintenance study CT-P10 1.3	rheumatoid arthritis	122 (Switched to CT-P10: 201)	51	-	1531
CT-P10 3.2 (Part 2)	rheumatoid arthritis	161	60	151	372
CT-P10 3.3 (Part 2)	AFL	70	-	70	140
Total		3541	111	221	6661

1 There were 20 patients received both MabThera and CT-P10 in Studies CT-P10 1.1 and CT-P10 1.3, respectively.

Safety

Safety studies in this submission included two ongoing, pivotal efficacy/safety studies (Study CT-P10 3.2 in patients with rheumatoid arthritis and Study CT-P10 3.3 in subjects with advanced follicular lymphoma) plus studies CT-P10 1.1, CT-P10 1.2 and CT-P10 1.3. The safety dataset is listed in Table 21 above. Patients were followed for up to 104 weeks in CT-P10 1.1 and 1.3, up to 48 weeks in CT-P10 3.2 and up to 24 weeks in CT-P10 3.3.

Rheumatoid arthritis

In the pooled analysis for the rheumatoid arthritis population (Studies CT-P10 1.1, CT-P10 1.3 and CT-P10 3.2), 199 (70.3%) of the patients treated with CT-P10 and 176 (67.2%) of the patients treated with the reference products (MabThera, Rituxan) experienced at least 1 treatment emergent AE. The most common types of treatment emergent AEs were infections (36.0% in the Total CT-P10 group versus 34.7% in the reference group) and infusion related reactions. A higher incidence of treatment-related infusion related reaction was reported with CT-P10 (16.6%) versus reference products (10.7%) in the pooled rheumatoid arthritis dataset (this is discussed in more detail below). Treatment emergent SAEs were reported in 29 (10.2%) of the patients in the Total CT-P10 group and 23 (8.8%) of the reference group, but only 3 (1.1%) in the Total CT-P10 group and 8 (3.1%) in the reference group were considered by the investigators to be related to the study drug. The frequency of patients who discontinued due to drug-related AEs was low and similar between the treatment groups. The most commonly reported laboratory abnormality was neutropenia. In the pooled analysis, neutropenia was reported in 1.4% (4 of 283) of patients in the Total CT-P10 group and 2.3% (6 of 262) of subjects in the reference group.

The reported difference in incidence of infusion related reaction in the rheumatoid arthritis studies (Table 22) was influenced by a lower than expected incidence of infusion related reaction in the Rituxan group (7.9%) in Study CT-P10 3.2 compared to CT-P10 (20.5%) and MabThera (21.7%). This result for Rituxan in Study CT-P10 3.2 is inconsistent with published historical data for rituximab (infusion related reaction around 20%). Outcomes for infusion related reaction in all other CT-P10 studies were consistent with the comparator, leading the evaluator to conclude that the low rate of infusion related reaction for Rituxan in Study CT-P10 3.2 was likely a chance finding.

Table 22: Summary of infusion related reactions in CT-P10 clinical trials (Safety population)

	Study CT-P10 3.2 (Main Study Period)			Study CT-P10 1.1		Study CT-P10 1.3		Study CT-P10 3.3	
	CT-P10 (N=161)	Rituxan® (N=151)	MabThera® (N=60)	CT-P10 (N=102)	MabThera® (N=51)	CT-P10 maintenance (N=38)	Switched from MabThera® (N=20)	CT-P10 (N=70)	Rituxan® (N=70)
No. of Events	**39**	**15**	**15**	**27**	**15**	**1**	**1**	**22**	**21**
No. (%) of patients with ≥ 1 IRR	**33 (20.5)**	**12 (7.9)**	**13 (21.7)**	**20 (19.6)**	**10 (19.6)**	**1 (2.6)**	**1 (5.0)**	**16 (22.9)**	**17 (24.3)**
Related	**33 (20.5)**	**12 (7.9)**	**13 (21.7)**	**20 (19.6)**	**10 (19.6)**	**1 (2.6)**	**1 (5.0)**	**15 (21.4)**	**17 (24.3)**
Grade 1	16 (9.9)	3 (2.0)	6 (10.0)	11 (10.8)	4 (7.8)	1 (2.6)	0	4 (5.7)	6 (8.6)
Grade 2	15 (9.3)	9 (6.0)	7 (11.7)	8 (7.8)	6 (11.8)	0	1 (5.0)	9 (12.9)	11 (15.7)
Grade 3	2 (1.2)	0	0	1 (1.0)	0	0	0	2 (2.9)	0
Unrelated	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (1.4)**	**1 (1.4)**
No. (%) of patients with ≥ 1 serious IRR	0	0	0	1 (1.0)	0	0	0	1 (1.4)	0
No. (%) of patients with ≥ 1 IRR leading to discontinuation	2 (1.2)	3 (2.0)	1 (1.7)	2 (2.0)	0	0	0	1 (1.4)	0
Number (%) of patients with ≥ 1 IRR requiring any treatment	15 (9.3)	7 (4.6)	6 (10.0)	10 (9.8)	6 (11.8)	0	1 (5.0)	13 (18.6)	16 (22.9)

In the 20 subjects who switched from MabThera to CT-P10 in Study CT-P10 1.3, there was no overt change to the safety profile with regard to the incidence and types of AEs.

Advanced follicular lymphoma

The safety dataset for this patient population is limited to 24 weeks of treatment follow-up in 140 subjects (70 in each treatment group). Similar proportions of subjects in each treatment group (CT-P10 and Rituxan) reported AEs (80.0 to 82.9%) and treatment related AEs (48.6 to 52.9%). The most frequently reported AEs in the CT-P10 treatment group were neutropaenia (24 (34.3%) patients), infusion related reaction (16 (22.9%) patients) and constipation (12 (17.1%) patients).

In Study CT-P10 3.3, the sponsor explained the higher rate of neutropaenia with CT-P10 (34.3%) compared to Rituxan (22.9%) based on the higher incidence of bone marrow

involvement at baseline in the CT-P10 group (64.3% versus 47.1% for Rituxan). Among the patients reported to experience neutropaenia in Study CT-P10 3.3, 18 of 24 (75%) subjects in the CT-P10 group and 7 of 16 (43.8%) patients in the Rituxan arm had bone marrow disease at baseline. This explanation was accepted by the evaluator. The incidence and severity of neutropaenia in the rheumatoid arthritis studies was comparable for all three formulations.

The clinical evaluator concluded that the overall safety profile of CT-P10 is similar to that of the reference product. The types and frequencies of AEs were in line with those reported for the reference product in the rheumatoid arthritis and NHL study populations. No new safety signals have emerged from the submitted dataset. The submitted dataset is limited to 24 to 48 weeks of treatment follow up for the majority of subjects, so ongoing safety data collection is important.

Immunogenicity

In the rheumatoid arthritis population in Study CT-P10 3.2, a lower percentage of CT-P10 treated subjects had positive anti-drug antibodies at Week 24 (14.9%; 24 of 161) compared to the reference products (26.7% (16 of 60) with MabThera and 21.9% (33 of 151) with Rituxan). There was a very low incidence of neutralising antibodies across the treatment groups. In the lymphoma population in Study CT-P10 3.3, no significant differences in anti-drug antibodies and neutralising antibody status were observed up to 24 weeks. The clinical relevance of anti-drug antibodies remains uncertain with no clear association with infection risk, infusion related reaction or other significant safety concern.

Risk management plan

The sponsor has submitted EU-RMP (version 7.0, date 18 May 2017, data lock point 26 October 2016) with Australian Specific Annex (ASA) (version 2.0, October 2017).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 17 above. The clinical evaluator has advised that the Summary of Safety Concerns in the RMP is satisfactory.

The additional pharmacovigilance proposed for the specified safety concerns and missing information consists of three clinical studies (CT-P10 3.2, CT-P10 3.3, CT-P10 3.4) and targeted follow-up questionnaires. The sponsor has committed to update the RMP and ASA to incorporate results of the ongoing clinical studies.

The additional risk minimisation proposed to address specified safety concerns consists of healthcare professional and patient educational materials and a Patient Alert Card (PAC).

The RMP evaluator recommends the following condition of registration:

> Implement EU-RMP (version 7.0, date 18 May 2017, data lock point 26 October 2016) with Australian Specific Annex (version 2.0, October 2017) and any future updates.

Discussion

Quality and nonclinical evaluations

The comparability of CT-P10 with EU-sourced MabThera, US-sourced Rituxan and Australian-sourced MabThera has been satisfactorily established through comprehensive comparability testing and bridging studies. The quality and non-clinical evaluators have no objection to the registration of Truxima based on biosimilarity to MabThera, provided GMP certification is complete.

Pharmacology

Pharmacokinetic and pharmacodynamic data from studies involving more than 300 patients with rheumatoid arthritis and more than100 patients with advanced follicular lymphoma, have satisfactorily demonstrated pharmacokinetic and pharmacodynamic equivalence of CT-P10 with MabThera and Rituxan.

Efficacy

Study CT-P10 3.2 demonstrated equivalent efficacy to MabThera and Rituxan for the rheumatoid arthritis indication. This is supported by efficacy data from Studies CT-P10 1.1 and CT-P10 1.3 up to 104 weeks for the rheumatoid arthritis indication. The x-ray data is considered sufficient to support the claim of radiographic benefit in the rheumatoid arthritis indication. Study CT-P10 3.3 demonstrated non-inferior efficacy to Rituxan for the lymphoma indication based on overall response rate (1999 IWG criteria) which is considered an acceptable endpoint for this submission.

Safety

The size of the safety population and duration of exposure were sufficient to allow adequate characterisation of the safety profile. The overall safety profile of CT-P10 is comparable to that of MabThera. Safety risks include infusion related reactions, serious infection and neutropenia. Differences in the incidence of infusion related reactions in the rheumatoid arthritis dataset and neutropaenia in Study CT-P10 3.3 were addressed by additional analyses and explanation from the sponsor. No new safety signals have emerged from the submitted dataset to indicate a change to the established risk profile of rituximab.

Immunogenicity

Immunogenicity of CT-P10 is considered comparable to MabThera. In the rheumatoid arthritis population in Study CT-P10 3.2, a lower percentage of CT-P10 treated subjects had positive anti-drug antibodies at Week 24 (14.9%) compared to the reference products (26.7% with MabThera and 21.9% with Rituxan). There was a very low incidence of neutralising antibodies across the treatment groups. No significant differences in anti-drug antibodies and neutralising antibody status were observed in the lymphoma population.

Switching between rituximab formulations

The submission provided limited data on subjects switching from one formulation to another. There were 20 subjects who were treated with CT-P10 in Study CT-P10 1.3 after receiving MabThera in Study CT-P10 1.1. No significant difference in B-cell responses was observed between the CT-P10 maintenance and switch cohorts over the whole study period (up to 2 years). Efficacy data (ACR20 and DAS28/EULAR responses) were also similar in the switch cohort compared to the CT-P10 maintenance cohort. There was no notable difference in the safety profile in the switch cohort of 20 subjects.

Extrapolation to all approved MabThera indications

The clinical studies provided in this submission provide evidence of comparable efficacy of CT-P10 compared to reference products for an autoimmune indication (rheumatoid arthritis) and an oncological indication (advanced follicular lymphoma). The evaluators have concluded that the pre-clinical and clinical comparability data and the supporting references and scientific justification provide sufficient evidence to extrapolate the treatment indications for CT-P10 to all approved MabThera indications.

RMP

The risk management strategies detailed in the RMP and ASA submitted with the sponsor's response are satisfactory.

Trade name

It is noted that the proposed trade name [information redacted] has been approved in the EU. It is also noted that a concern has not been raised during the evaluation process regarding the acceptability of this proposed trade name (in Australia). [Information redacted] could be viewed as having a promotional quality. Further comment is requested from the sponsor regarding this trade name.

Data deficiencies

No direct evidence of clinical efficacy in CLL, MPA and GPA was provided in this submission, but the comparability data and justification in this submission are considered sufficient to support extrapolation to these indications.

There is limited data on switching between different rituximab formulations. 20 subjects with rheumatoid arthritis switched from MabThera to CT-P10 (single 1-way treatment switch) in Study CT-P10 1.3.

The submission contains safety data up to 48 weeks for the majority of subjects, and up to 104 weeks for 35 subjects in studies CT-P10 1.1 and 1.3. Additional safety data from the maintenance study phase of Study CT-P10 3.3, the extension period of Study CT-P10 3.2 and the planned new trial in patients with low tumour burden lymphoma (Study CT-P10 3.4) will contribute to the long term safety dataset.

Conclusion

GMP certification (at the time of the Delegates overview) is not yet finalised for three manufacturing steps but the evaluator is otherwise satisfied that there are no objections to approval on quality grounds. There are no objections to approval from the nonclinical and clinical evaluators. The evaluators have concluded that the submission has adequately demonstrated biosimilarity with the Australian reference product, MabThera.

The development program for CT-P10 was guided by EU requirements for biosimilar medicines. The submission included comprehensive physicochemical, pharmacology, nonclinical and clinical comparability studies between CT-P10, EU-sourced MabThera and US-sourced Rituxan. Additional bridging studies comparing EU-sourced and Australian-sourced MabThera were provided to support the claim of biosimilarity with the Australian reference product. Clinical studies support comparable efficacy, safety and immunogenicity of CT-P10 to MabThera in patients with rheumatoid arthritis and advanced follicular lymphoma. These studies have validity to contemporary Australian practice and internationally accepted rheumatoid arthritis and lymphoma treatment guidelines. On the basis of biosimilarity and relevant scientific justification, extrapolation to all approved MabThera indications is considered appropriate.

There are no objections to registration of Truxima provided the outstanding GMP clearances are issued. At this stage, subject to the advice of the ACM, finalisation of the PI, further discussion re the name [information redacted] and resolution of GMP clearance, but this application for a new biosimilar of rituximab could be approved.

Conditions of registration

The following are proposed as conditions of registration:

- Implement EU RMP version 7.0 (date 18 May 2017; DLP 26 October 2016) and ASA version 2.0 (date October 2017), and any future updates.
- Submit the final Clinical Study Reports for the two on-going Phase III studies (Studies CT-P10 3.2 and 3.3) as well as the interim and final data for Study CT-P10 3.4 (proposed Phase III trial in patients with low tumour burden follicular lymphoma) as category 1 submissions when available.

- It is a condition of registration that all batches of Truxima rituximab (rch) and (information redacted) rituximab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Truxima rituximab (rch) and (information redacted) rituximab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Questions for the sponsor

1. Please advise of any changes in the status of the current submissions to USA, Singapore, Switzerland and Canada.
2. Please comment on the proposed trade name [information redacted], particularly with regard to whether the name has promotional qualities.

Risk-benefit analysis

Delegate's considerations

The risk management strategies detailed in the RMP and ASA submitted with the sponsor's response are satisfactory.

Issues arising from this submission include:

- GMP certification is not yet finalised for three manufacturing steps.
- The submission provided clinical data for the rheumatoid arthritis and advanced follicular lymphoma indications. The guidelines for biosimilars allow extrapolation to other indications based on the overall evidence of comparability, including structure, pharmacodynamics, pharmacokinetics and efficacy. The evaluators have concluded that extrapolation to the other approved MabThera indications is appropriate based on the comparability data and scientific justification.
- There was a higher incidence of infusion-related reactions in the rheumatoid arthritis dataset and neutropaenia in Study CT-P10 3.3, but additional analyses and explanations provided by the sponsor are considered to have adequately addressed these concerns.
- Further comment is sought from the sponsor regarding the name [information redacted].

Proposed action

The Delegate had no reason to say, at this time, that this application for Truxima should not be approved for registration, subject to the advice of the ACM and GMP clearance.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACM have any concerns regarding the comparability of Truxima and MabThera?
2. Is the ACM satisfied with the proposed extrapolation to all indications approved for MabThera?

3. Does the ACM have any concern with the proposed trade name (information redacted), noting that this name is approved in the EU?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor respectfully requests the ACM members to consider the discussions and materials presented. The sponsor firmly believes that this information will assist the ACM considering the summary of issues raised by the Delegate and provides information regarding the advice sought from the committee and will permit the committee to recommend approval of Truxima.

Clinical

The sponsor accepts and acknowledges the clinical evaluator's recommendation of approval of Truxima rituximab as a biosimilar of MabThera for all of the current approved treatment indications the reference product, including rheumatoid arthritis, NHL, CLL and ANCA associated vasculitis.

The sponsor highlights that the clinical evaluator determined that the dataset submitted demonstrated evidence that CT-P10 is therapeutically equivalent to MabThera in improving the signs and symptoms of active rheumatoid arthritis that are inadequately responding to methotrexate and been previously treated with anti-TNF drugs. In addition, CT-P10 showed comparable efficacy to Rituxan in adult patients with advanced follicular lymphoma (AFL), noting that the three formulations of Rituximab presented in the data, in terms of safety, appear clinically equivalent for the incidence and type of clinically significant safety concerns. The sponsor has committed to the TGA of the submission of the final Clinical Study Report for the ongoing clinical studies upon their completion.

Non-clinical

The sponsor acknowledges and agrees with the non-clinical evaluator's conclusion and recommendation that there are no nonclinical objections to the registration of Truxima based on the confirmation by the chemistry evaluator, that the EU-sourced MabThera is accepted to be identical or highly comparable to the Australian MabThera. Noting that there were no chemistry and manufacturing objections and recommended for approval.

Quality and manufacturing

The sponsor accepts and acknowledges the positive recommendation of the sponsor's rituximab as a biosimilar. The comparability of CT-P10 with EU-sourced MabThera, US-sourced MabThera (Rituxan) and Australian-sourced MabThera has been satisfactorily established through the comprehensive comparability testing and bridging studies. There are no objections to approval based on biosimilarity to MabThera.

The sponsor acknowledges the comments relating to outstanding GMP clearances for a number of the manufacturing sites. The delay has arisen due to later inspections occurring in late 2017 and request from the GMP team for the latest inspection reports which are expected to be issued by February 2018.

RMP

The sponsor acknowledges the comments that all recommendations have been satisfactorily addressed and confirms that the proposed wording of the condition of registration in relation to RMP is acceptable.

Sponsor's comments on the delegate's overview (summary of issues)

GMP certification

As per the Delegate's overview:

- *GMP certification is not yet finalised for three manufacturing steps.*

GMP clearances remain under assessment with TGA GMP clearance team at this time, however the sponsor are confident that all remaining clearances will be issued. As noted above the delay has arisen due to later inspections occurring in late 2017 and a request from the TGA GMP team for the latest inspection reports, which are expected to be issued by February 2018.

- *The submission provided clinical data for the rheumatoid arthritis and follicular lymphoma indications. The guidelines for biosimilars allow extrapolation to other indications based on the overall incidence of comparability, including structure, pharmacodynamics, pharmacokinetics and efficacy. The evaluators have concluded that extrapolation to the other approved MabThera indications is appropriate based on the comparability data and scientific justification.*

The sponsor acknowledges and agrees with the conclusions that adequate comparability has been submitted to support extrapolation to approved MabThera indications.

Compelling physicochemical and functional similarity was accomplished with CT-P10 versus MabThera and Rituxan together with the clinical data in rheumatoid arthritis and AFL patients, including pharmacokinetic/pharmacodynamic, efficacy, safety and immunogenicity similarity provide sufficient evidence in support of the quality, safety, and efficacy of CT- P10 being highly similar to MabThera and Rituxan with respect to all the indications.

A large number and wide range of orthogonal, highly sensitive methods were used to provide a meaningful algorithm to assess biosimilarity. The results of the similarity studies conclusively establish that CT-P10 and MabThera are highly similar in physicochemical attributes and all biological activities associated with known and putative functions and therapeutic effects. These comprehensive analyses have also shown that CT-P10 is highly similar to MabThera in primary structure, higher order structure, aggregate and monomeric purity, and post-translational modifications notwithstanding minor differences that have been demonstrated to have no clinically meaningful impact on efficacy and safety.

The extensive range of in vitro biological assays have conclusively demonstrated highly similar biological activities for CT-P10 and MabThera in functional assays, potency, and binding affinity related to putative mechanisms of action of rituximab in NHL, CLL, rheumatoid arthritis, GPA and MPA. Furthermore, an extensive range of biological assays for assessment of complement dependent cytotoxicity, antibody dependent cellular cytoxicity, antibody dependent cellular phagocytosis and apoptosis activities was carried and showed highly similar activities for CT-P10 and MabThera against healthy, NHL and CLL donor target B-cells.

Based on the comprehensive comparability exercise, which takes into consideration mechanism of action, structural analysis, functional assays and the clinical biosimilarity of pharmacokinetic, efficacy, safety and immunogenicity, the sponsor considers that there is sufficient scientific evidence to support extrapolation to all indications for which MabThera is authorised in Australia.

A summary of the information provided within the dossier was provided as an annex which supported the evaluators' conclusions that extrapolation to all MabThera Indications is appropriate and has been adequately demonstrated.

- *There was a higher incidence of infusion-related reactions in the rheumatoid arthritis dataset and neutropenia in Study CT-P10 3.3, but additional analyses and explanations provided by the sponsor are considered to have adequately addressed these concerns.*

The sponsor acknowledges and agrees with the TGA conclusion that the data and responses submitted have adequately addressed the initial concerns relating to infusion related reaction and neutropenia.

There were no notable differences among the treatment groups in regard to seriousness, severity and clinical characteristics of the reported infusion related reactions. All captured events of infusion related reactions in Study CT-P10 3.2 were mild (grade 1) or moderate (grade 2) with the exception of 2 patients in the CT-P10 group who experienced severe (grade 3) events. All events were recovered without sequelae.

Overall incidences of infusion related reactions were similar between the treatment groups throughout all CT-P10 clinical trials except for rheumatoid arthritis Study CT-P10 3.2. In rheumatoid arthritis Study CT-P10 1.1, the proportion of patients experiencing infusion related reactions were similar; 20 of 102 (19.6%) and 10 of 51 (19.6%) in CT-P10 and MabThera group, respectively. In rheumatoid arthritis extension Study CT-P10 1.3, one patient in each treatment groups reported infusion related reaction; 1 of 38 (2.6%) patient and 1 of 20 (5.0%) patient in CT-P10 and Switched from MabThera group, respectively. Likewise, in the Advanced follicular lymphoma Study CT-P10 3.3, 16 of 70 (22.9%) and 17 of 70 (24.3%) patients in the CT-P10 and Rituxan groups respectively, experienced infusion related reactions showing similar distribution between the two treatment groups.

Of note, during the Main Study Period in Study CT-P10 3.2, (up to Main Week 48), a lower proportion of patients with at least 1 event of infusion related reaction in the Rituxan group was noted, whereas results in other treatment groups were generally similar. A total of 58 of 372 (15.6%) patients experienced at least 1 infusion related reaction: 33 of 161 (20.5%), 12 of 151 (7.9%) and 13 of 60 (21.7%) patients in the CT-P10, Rituxan and MabThera groups, respectively. The incidence rates of infusion related reactions in the Study CT-P10 3.2 (main study period) were in line with the frequencies of acute infusion related reactions reported in rheumatoid arthritis patients who were pre-treated with IV corticosteroid in historical studies with rituximab, considering all of the patients treated in Study CT- P10 3.2 (main study period) received premedication of an antipyretic (for example, paracetamol), an antihistamine (for example, chlorpheniramine) and/or a glucocorticoid (for example, methylprednisolone) before each infusion of the study drug. In the DANCER study (Study WA17043), medically-reviewed acute infusion reactions following the first infusion of the first treatment course occurred in 18 of 65 (28%) patients who received rituximab (1,000 mg) without IV corticosteroid premedication compared to 24 of 127 (19%) patients who received rituximab with IV corticosteroid premedication (MabThera RMP 2014 (EMA ASK-7379)).

The incidence of infusion related reactions in Study CT-P10 3.2 was compared with those from rituximab historical randomized controlled trials in rheumatoid arthritis patients. Overall, there was no clinically meaningful difference in the incidence of infusion related reactions in CT-P10 clinical trials. It was found that the incidence of infusion related reactions in the Rituxan group of Study CT-P10 3.2 is relatively low compared to CT-P10 and MabThera treatment groups which showed consistency with historical data, but it is even notably lower than the historical data. Therefore, it is concluded that the observed trend for a lower incidence of infusion related reactions with Rituxan is likely to be a chance finding specifically confined to Study CT-P10 3.2 and not replicated in other studies with CT-P10, which showed a similar proportion of patients with infusion related reactions between the CT-P10 and reference products.

Regarding neutropaenia, there were no new safety signals identified throughout CT-P10 clinical studies in regards to TEAE of neutropaenia with the numerical variation in Study CT-P10 3.3 in the percentage of patients with neutropenia considered likely driven by uneven distribution of bone marrow involvement between the treatment groups. The proportion of patients who experienced TEAE of neutropaenia were similar between the treatment groups in CT-P10 rheumatoid arthritis studies. Study CT-P10 3.2 main study period: 1 of 161 (0.6%) patients, 3 of 151 (2.0%) patients, and 1 of 60 (1.7%) patients in the CT-P10, Rituxan, and MabThera group respectively; Study CT-P10 1.1: 2 of 102 (2.0%) patients and 2 of 51 (3.9%) patients in the CT-P10 and MabThera group, respectively; none reported in Study CT-P10 1.3. The proportion of patients who experienced treatment emergent AEs of leukopaenia and neutrophil count decreased in the rheumatoid arthritis studies were also similar between the treatment groups without any clinically meaningful differences.

- *Further comment is sought from the sponsor regarding the name [information redacted]*

As noted by the Delegate the tradename (information redacted) has been approved in the EU with no concerns raised and no issues where raised during the evaluation process. This medicine is only available as a Prescription Only Medicine and administered by a Health Care Professional. The sponsor is of the firm opinion that this tradename is not promotional and certainly in the setting of prescription and administration this concern if deemed valid, is negated for this biosimilar medicine.

Sponsor's comments to advice sought

1. *Does the ACM have any concerns regarding the comparability of Truxima and MabThera?*

The sponsor has conducted comprehensive comparability exercises, which took into consideration mechanism of action, structural analysis, functional assays and the clinical biosimilarity of pharmacokinetic, efficacy, safety and immunogenicity; the sponsor considers that there is sufficient scientific evidence to support comparability and extrapolation to all indications for which MabThera is authorised in Australia. The sponsor notes that the TGA evaluations (quality, nonclinical and clinical) have concluded the same.

CT-P10 has been developed as a similar biological medicinal product to the innovator product MabThera (rituximab) for intravenous (IV) use which is also marketed under the name of Rituxan in the US. CT-P10 drug product was designed to be highly similar to its reference medicinal product (RMP), MabThera. CT- P10 and MabThera are identical with respect to pharmaceutical form, concentration and composition, and route of administration.

As outlined in the relevant CHMP guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1: Guideline on similar biological medicinal products, EMA/CHMP/BWP/247713/2012: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) and EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues) 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 characterisation of CT-P10 relative to its RMP. 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 objective of the 3-way similarity study was to establish the similarity of CT-P10 with the RMP, MabThera by testing multiple batches of the products and analysing the results using quantitative ranges, where possible. The similarity studies were designed carefully

following the various CHMP guidelines, as noted above, specific to the subject of similarity testing for biosimilar products, as well as the principles of similarity as discussed in ICH Q5E (Note for guidance on biotechnological/biological products subjected to changes in their manufacturing processes).

The results of the 3-way study confirmed similarity between CT-P10, MabThera and Rituxan demonstrating the following:

- Identical primary structure shown using methods such as amino acid analysis, molar absorptivity, N- terminal sequencing, C-terminal sequencing, peptide mapping by HPLC, peptide mapping by LC-MS, and determination of intact mass;
- Highly similar secondary and higher order structure using methods such as Fourier Transform Infra- Red spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Circular Dichroism (CD), free thiol content, and disulphide bonding;
- Similar post-translational modifications included deamidation, oxidation and C-terminal lysine variants which were all observed at low levels for all batches and were similar between the three products;
- Highly similar glycosylation profile with a small difference in Man5 content which was found to have no impact on the Fab- and Fc-related biological activities and the clinical activity of the product;
- Highly similar degradation and stability profile.

A more detailed summary of the results of the comparability exercises was provided with this response (not reproduced here).

The comparability of Truxima and MabThera is also further supported from both non-clinical and clinical perspectives as highlighted in; Information on Extrapolation (provided with the response but not reproduced here).

In conclusion, a large number and wide range of orthogonal, highly sensitive methods were used to provide a meaningful biosimilarity. These comprehensive analyses have shown that CT-P10 is highly similar to MabThera in primary structure, higher order structure, purity / impurity, charged variants and glycosylation not withstanding minor differences that have been demonstrated to have no clinically meaningful impact.

A variety of in vitro biological assays have conclusively demonstrated highly similar biological activities for CT-P10 and MabThera in functional assays, potency, and binding affinity related to putative mechanisms of action of rituximab in NHL, CLL, rheumatoid arthritis, GPA and MPA. In addition, high similarity between MabThera and Rituxan has also been established. Thus, CT-P10 and MabThera will have highly similar therapeutic effects across all indications for which MabThera is approved in Australia.

2. Is ACM satisfied with the proposed extrapolation to all indications approved for MabThera?

Refer to sponsor's comments to Summary of Issues/s above.

3. ***Does ACM have any concern with the proposed trade name [information redacted], noting that this name is approved in the EU?***

Refer to sponsors comments to Summary of Issues/s) and below (Sponsor's Response to Delegates Questions).

Sponsor's responses to Delegate's questions

Question 1

> *Please advise any changes in the status of the current submissions to USA, Singapore, Switzerland and Canada?*

The sponsor confirms that there are currently no status updates for submissions currently under review in USA, Singapore, Switzerland or Canada.

Question 2

> *Please comment on the proposed trade name [information redacted], particularly with regard to whether the name has promotional qualities?*

The sponsor is of the firm opinion that the proposed trade name (information redacted) does not contain promotional qualities. The tradename is to be used globally and has been approved in the EU as noted by the Delegate with no objections. The sponsor notes that the quality evaluator had no objection to the proposed tradename and neither the nonclinical nor clinical evaluators raised the tradename as a concern during the evaluation process. As stated above in sponsors comments to Summary of Issues/s this medicine is only available as a Prescription Only Medicine and administered by a Health Care Professional. The sponsor is of the firm opinion that this tradename is not promotional and certainly in the setting of prescription and administration this concern if deemed valid, is negated for this biosimilar medicine.

We trust that the TGA and the ACM will find this acceptable and find no objections to the use of the proposed trade name [information redacted].

Conditions of registration

The sponsor acknowledges the TGA's proposed conditions of registration.

Advisory Committee Considerations[23]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Truxima solution for infusion containing 500 mg/50 mL, 100 mg/10 mL of Rituximab to have an overall positive benefit-risk profile for the proposed indications, which are identical to MabThera:

> *Non-Hodgkin's Lymphoma*
>
> *Truxima is indicated for treatment of patients with:*
>
> - *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,*
> - *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,*
> - *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.*
>
> *Chronic Lymphocytic Leukaemia*

[2323] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Truxima is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

Truxima (rituximab) 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 at least one tumour necrosis factor (TNF) inhibitor therapy.

Truxima has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

Truxima in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with rituximab have not been established.

In making this recommendation the ACM noted:

- Some GMP clearances for these products are still not finalised[24]

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. ***Does the ACM have any concerns regarding the comparability of Truxima and MabThera?***

The committee considered the physicochemical, pharmacological, clinical and safety properties of Truxima to be very similar to MabThera and was of the view that Truxima was highly comparable to MabThera.

2. ***Is the ACM satisfied with the proposed extrapolation to all indications approved for MabThera?***

Two pivotal Phase III studies, one in patients with active rheumatoid arthritis and another with patients with advanced follicular lymphoma, were submitted. In applying the biosimilar principles, the committee considered that it was reasonable to extrapolate equivalence to include all indications approved for MabThera to Truxima, including vasculitis.

3. ***Does the ACM have any concern with the proposed trade name [information redacted], noting that this name is approved in the EU?***

The ACM was of the view that the trade name [information redacted] may be considered promotional and was not appropriate. The committee preferred the trade name Truxima.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

[24] Clarification: All GMP issues were resolved prior to registration.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Truxima/ Ritemvia rituximab concentrate for intravenous infusion 100 mg in 10 mL or 500 mg in 50 mL, indicated for:

Non-Hodgkin's Lymphoma

Truxima/Ritemvia is indicated for treatment of patients with:

CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,

CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,

CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic Lymphocytic Leukaemia

Truxima/Ritemvia is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

Truxima/Ritemvia (rituximab) 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 at least one tumour necrosis factor (TNF) inhibitor therapy. Truxima/Ritemvia has been shown to reduce the rate of progression of joint damage as measured by xray when given in combination with methotrexate.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

Truxima/Ritemvia in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with rituximab have not been established.

Specific conditions of registration applying to these goods

1. The Truxima and Ritemvia EU-Risk Management Plan (RMP) (version 7.0; date 18 May 2017; DLP 26 October 2016), with Australian Specific Annex (version 2.0; date October 2017), included with submission PM-2017-00695-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. Any changes to which you have agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.
2. All batches of Truxima and Ritemvia rituximab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   Each batch of Truxima and Ritemvia rituximab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

3. The following clinical study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission:
    - Final clinical study report for CT-P10 3.2
    - Final clinical study report for CT-P10 3.3
    - Interim and final clinical study report for CT-P10 3.4

Attachment 1. Product Information

The PI for Truxima approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for Ritemvia is identical except for the product name.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au