27 June 2013
EMA/CHMP/589317/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Remsima

International non-proprietary name: Infliximab

Procedure No. EMEA/H/C/002576/0000

Note

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

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Product information

Name of the medicinal product:	Remsima
Applicant:	Celltrion Healthcare Hungary Kft. 1023 Budapest, Regus Óbuda Gate Árpád Fejedelem útja 26-28 Hungary
Active substance:	Infliximab
International Nonproprietary Name/Common Name:	Infliximab
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, tumour necrosis factor alpha (TNF_{α}) inhibitors (L04AB02)
Therapeutic indications:	<u>Rheumatoid arthritis</u> Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate. • adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated. <u>Adult Crohn's disease</u> Remsima is indicated for: • treatment of moderate to severe, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. • treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). <u>Paediatric Crohn's disease</u> Remsima is indicated for treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy. <u>Ulcerative colitis</u> Remsima is indicated for treatment of moderate to severe active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

	<u>Paediatric ulcerative colitis</u> Remsima is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. <u>Ankylosing spondylitis</u> Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy. <u>Psoriatic arthritis</u> Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Remsima should be administered • in combination with methotrexate • or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the X-ray in patients with polyarticular symmetrical subtypes of the disease. <u>Psoriasis</u> Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

Executive Summary

Tumour Necrosis-Factor-alpha (TNFα) inhibition is an important treatment option for several chronic inflammatory autoimmune disorders in rheumatology and gastroenterology. TNFα is a multipotent cytokine that occurs in monomeric and trimeric soluble and transmembrane forms. It exhibits a wide spectrum of activity, including coordinating host immune and inflammatory response to infectious, malignant and autoimmune conditions. TNFα exerts its biological functions by binding to the TNF receptor, of which two types have been identified: TNF-R1 and TNF-R2. TNF-R1 is expressed in most tissues and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF, whereas TNF-R2 is found only in cells of the immune system.

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα. TNFα receptor activation is prevented by infliximab through binding to TNFα, thereby neutralizing the biological activity of TNFα. This monoclonal antibody was first authorised in the EU in August 1999 under the invented name of Remicade. It is currently approved for the following indications: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult and paediatric Crohn's disease and adult and paediatric ulcerative colitis.

In June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Remsima as a biosimilar medicinal product containing infliximab. This is the first time that such recommendation is given in the European Union for a biosimilar monoclonal antibody. The therapeutic indications as well as the dosing regimen are the same as those of Remicade; the pharmaceutical form (powder for concentrate for solution for infusion) and strength (100 mg infliximab per vial) are also the same.

In order to support this authorisation, the results of an extensive comparability exercise between the two products were presented. Demonstration of comparability via a thorough development programme included quality, nonclinical and clinical data and is key to the evaluation of a biosimilar medicinal product.

As part of the comparability exercise it was shown that all major physicochemical characteristics and biological activities of Remsima were comparable to those of Remicade. The CHMP noted a small difference in the amount of afucosylated infliximab, translating into a lower binding affinity towards specific Fc receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) activity in the most sensitive ADCC assay. This difference was, however, not considered clinically meaningful, as it did not affect the activities of Remsima in experimental models regarded as more relevant to the pathophysiological conditions in patients.

The clinical data demonstrating similarity between Remsima and Remicade consisted of two main clinical trials: a pivotal pharmacokinetic study in patients with ankylosing spondylitis (AS) (Study CT-P13 1.1) and a pivotal efficacy and safety study in patients with active rheumatoid arthritis (RA) (Study CT-P13 3.1). The pharmacokinetic trial in AS patients showed, at the dose of 5 mg/kg, comparable profiles between Remsima and Remicade at steady state (after 5 doses) with the 90% confidence intervals of the geometric means ratios (%) of both primary parameters $C_{max,ss}$ and AUC_{τ} contained within the pre-specified bioequivalence interval: AUC_{τ}:104.10 (93.93-115.36) and $C_{max,ss}$: 101.47 (94.57-108.86). In addition, the results of the main secondary pharmacokinetic parameters such as $T_{max,}$ $C_{min,ss}$, $T_{½}$, CL_{ss}, V_{ss} between Weeks 22 and 30, as well as C_{max} and C_{min} after the 9 treatment doses were also comparable in the Remsima and Remicade treatment arms, providing further evidence of a similar PK behaviour. Additional supportive data regarding the similarity at the dose of 3 mg/kg were provided from the second main study. The efficacy and safety trial in RA patients achieved its primary endpoint since the 95% confidence interval for the difference in the ACR20 response rate at Week 30 was contained within the

predefined equivalence margin (± 15%) in both the all-randomised (95% CI: -0.06, 0.10) and Per Protocol populations (95% CI: -0.04, 0.12). At week 30, the results of the secondary endpoints (in particular ACR50 and ACR70, decreases in DAS28, SDAI and CDAI, increases in SF-36) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 54. Additional supportive efficacy data were provided in another indication by the PK study CT-P13 1.1 conducted in AS patients. The efficacy results were comparable between treatment arms up to Week 54.

The evaluation of the safety profile of the biosimilar medicinal product was supported mainly by the results from the two clinical studies mentioned above. The type and incidence of adverse drug reactions observed with Remsima and Remicade in the respective studies were generally similar and no new safety concern was identified. There were no marked differences in the immunogenicity profile of the two products up to 54 weeks and the impact of antibodies on efficacy and safety was comparable. A numerical imbalance in serious adverse events was observed in the study CT-P13 3.1 with a higher number of serious infections, including active tuberculosis. However, the numbers were low and the CHMP, based on a thorough review of all available evidence, was of the opinion that the observed difference was most likely a chance finding. It was also noted that there is no plausible explanation from a mechanistic point of view for a difference in host defence. Serious infections, including tuberculosis will be closely monitored on a longer term and in larger cohorts of patients as part of the post-marketing setting through several registries conducted in different patient populations as described in the risk management plan, such as the British Society For Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA), the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) and other Applicant's sponsored registries. Rare adverse events known to Remicade, such as malignancies and lymphoproliferative disorders will also be closely monitored as part of these registries.

Based on the robust comparisons of the physicochemical and *in vitro* and *ex vivo* biological analyses, Remsima was considered biosimilar to the reference product Remicade. These data, in combination with clinical data demonstrating pharmacokinetic and therapeutic equivalence in rheumatology conditions, allow for extrapolation to all other indications of Remicade. In addition, the Applicant will conduct a randomised, double-blind, parallel-group comparative study between Remsima and Remicade in patients with active Crohn's disease.

The CHMP concluded that the benefit/risk balance of Remsima as a biosimilar product to Remicade is positive. Several post-authorisation studies and registries, as detailed in the risk management plan, will provide further long-term efficacy data, including in the treatment of inflammatory bowel diseases, and further characterise the long-term safety profile of Remsima.

Table of contents

List of abbreviations

6-MP	6-Mercaptopurine
ACR	American College of Rheumatology
ACR20	20% improvement according to the ACR criteria
ACR50	50% improvement according to the ACR criteria
ACR70	70% improvement according to the ACR criteria
ADCC	Antibody-dependent cell-mediated cytotoxicity
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
AUC	Area under the concentration-time curve
AUC_T	Area under the concentration-time curve over the dosing interval
AZA	Azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
biw	Twice a week
BLA	Biologic License Application
BMWP	Biosimilar Medicinal Products Working Party
bw	Body weight
CD	Crohn's disease
CDAI	Clinical disease activity index
CDC	Complement-dependent cytotoxicity
cfu	Colony forming unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Total body clearance
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Maximum serum concentration
CHMP	Committee for Human Medicinal products
CRP	C-reactive protein
CSR	Clinical study report
DAS	Disease activity score
db	Double-blind
DMARD	Disease-modifying anti-rheumatic drugs
EGA	Evaluator's global assessment
EM(E)A	European medicines Agency
enr	Enrolled
eow	Every other week
EPCB	End-of-production cell bank
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	The European League Against Rheumatism
EWP	Efficacy Working Party
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	General health
h	Hour(s)
HAQ	Health assessment questionnaire
HCCF	Harvested cell culture fluid
HCP	Host cell protein
HMW	High molecular weight
i.v.	Intravenous
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G, subtype 1
JIA	Juvenile idiopathic arthritis
kg	Kilogram
L	Litre
LC-MS	Liquid chromatography – mass spectrometry
LMW	Low molecular weight

LRV	Log_{10} reduction value
mAb	Monoclonal antibody
max	Maximum
mc	Multicentre
MCB	Master Cell Bank
mg	Milligram
min	Minimum
mL	Millilitre
MTX	Methotrexate
N, n	Number
n.r.	Not reported
N/A	Not applicable
ND	No data available
NSAID	Non-steroid anti-inflammatory drugs
PD	Pharmacodynamic(s)
PGA	Patient's global assessment
pI	Isoelectric point
PI	Product information
PK	Pharmacokinetic(s)
PP	Per-protocol
Ps	Psoriasis
PsA	Psoriatic arthritis
PUVA	Psoralen combined with ultraviolet A (UVA)
q4	Every 4 weeks
q8	Every 8 weeks
q6	Every 6 weeks
QoL	Quality of life
qw	Every week
ra	Randomised
RA	Rheumatoid arthritis
RF	Rheumatoid factor
Rt	Retention time
s.c.	Subcutaneous
SD	Standard deviation
SDAI	Simplified disease activity index
SE	Standard error
SF-36	Medical outcomes study short-form health survey
SJC	Swollen joint count
SmPC	Summary of product characteristics
SOC	System organ class
SPR	Surface Plasmon Resonance
STD	Study
sTNF	Soluble tumour-necrosis factor alpha
$T_{½}$	Terminal elimination half life
TB	Tuberculosis
TJC	Tender joint count
tm	Transmembrane
tmTNF	Membrane bound tumour necrosis factor
TNF	Tumour necrosis factor
TNFR	Tumour-necrosis factor receptor
TNFß	Tumour-necrosis factor beta
TNFα	Tumour-necrosis factor alpha
UC	Ulcerative colitis
USA	United States of America
VAS	Visual analogue scale
Vc	Volume of distribution in the central compartment
Vp	Volume of distribution in the peripheral compartment
V_{ss}	Volume of distribution at steady state
WCB	Working Cell Bank
WGET	Wegener's Granulomatosis Etanercept Trial
Wk(s)	Week(s)
y	Year(s)

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Celltrion Healthcare Hungary Kft. submitted on 1 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Remsima, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The Applicant applied for the following indications:

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Adult Crohn's disease

Remsima is indicated for:

- treatment of moderate to severe, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

Remsima is indicated for treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

Remsima is indicated for treatment of moderate to severe active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Remsima is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Remsima should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis

Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA (see section 5.1).

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The Applicant received scientific advices from the CHMP on 24 September 2009 and 17 December 2009. The scientific advices pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application. Remsima has been given a marketing authorisation in South Korea on 23 July 2012.

1.2. Manufacturers

Manufacturer of the active substance

CELLTRION Inc
13-6 Songdo-dong
Yeonsu-gu, Incheon, 406-840
Republic of Korea

Manufacturer responsible for batch release

Biotech Services International Limited
Biotec House, Central Park, Western Avenue
Bridgend Industrial Estate
Bridgend, CF31 3RT
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson

Co-Rapporteur: Janne Komi

- The application was received by the EMA on 01 March 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 16-19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 20 July 2012.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 16 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 28 December 2012.
- During the meeting on 7-10 January 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 14-17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 29 April 2013.
- During the meeting on 13-16 May 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues to all CHMP members on 14 May 2013.

- The Rapporteurs circulated the updated Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues to all CHMP members on 24 May 2013.
- During the CHMP meeting on 27-30 May 2013, outstanding issues were addressed by the Applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 27-30 May 2013, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the Applicant.
- The Applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 5 June 2013.
- During the meeting on 10-13 June 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the second List of Outstanding Issues to all CHMP members on 19 June 2013.
- During the meeting on 27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Remsima.

2. Scientific discussion

2.1. Introduction

Problem statement

Tumour necrosis-factor-alpha (TNFα) is a multipotent cytokine that occurs in monomeric and trimeric soluble and transmembrane forms. It is mainly produced by macrophages, as well as by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neural tissue. TNFα exhibits a wide spectrum of activity, including coordinating host immune and inflammatory response to infectious, malignant and autoimmune conditions. Large amounts of TNFα have been shown to be released in response to liposaccharide, other bacterial components and interleukin-1 (IL-1). Whereas initial TNFα expression in response to infection or injury is beneficial, sustained or excessive expression has been identified in several chronic inflammatory autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps), psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC).

TNFα causes its biological effects by binding to the TNF receptor, of which two types have been identified: a 55 kDa protein (p55, TNF-R1) and a 75 kDa protein (p75, TNF-R2). TNF-R1 is expressed in most tissues and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF, whereas TNF-R2 is found only in cells of the immune system.

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα. Infliximab prevents TNFα receptor activation by binding to TNFα, thereby neutralizing the biological activity of TNFα. Infliximab was first authorised in the EU on 13 August 1999 under the name of Remicade. It is currently approved for the following indications: RA, AS, Ps, PsA, CD and UC. In this similar biological application the Applicant applied for all approved Remicade indications.

About the Product

Remsima (also referred to as CT-P13 in the report) contains the active substance infliximab and has been developed as a similar biological medicinal product to the reference medicinal product Remicade. The

formulation development process for Remsima has been designed to replicate Remicade and both products are identical with respect to the pharmaceutical form, strength, composition and route of administration. Remsima drug product is a powder for concentrate for solution for infusion supplied at 100 mg infliximab per vial and contains the same excipients as Remicade. The powder has to be reconstituted with 10 mL of sterile water for injections resulting in a pH of approximately 7.2. The total volume of the reconstituted solution should then be diluted to 250 ml with sodium chloride 9 mg/ml (0.9%) solution for infusion. The product is administered as an intravenous infusion, usually over a 2-hour period. Depending on the indication, a loading dose regimen of 3 or 5 mg/kg at 0, 2 and 6 weeks may be followed by a maintenance dose regimen of the same dose every 6 or 8 weeks. The proposed therapeutic indications and posology for CT-P13 are identical to those for Remicade, to which similarity is claimed.

Type of application and aspects on development

The application is submitted under the Centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004, biotech medicinal product. This application is submitted in accordance with the following article in directive 2001/83/EC: Article 10(4): Similar biological application. The European reference medicinal product is Remicade (infliximab) 100 mg powder for concentrate for solution for infusion, MA numbers EU/1/99/116/001-005, MA holder Janssen Biologics B.V., authorised 13 August 1999.

An extensive comparability exercise is required to demonstrate that the similar biological product and the reference medicinal product already authorised in the Union have similar profiles in terms of quality, safety and efficacy. The evaluation of this clinical development programme of CT-P13 has specifically to consider the EU guidelines for similar biological medicinal products and also indication-specific guidelines (see list below).

Guideline	Document Reference
Guideline on Similar Biological Medicinal Products. CHMP, 2005	CHMP/437/04
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues. EMEA, 2006	EMEA/CHMP/BWP/49348/2005
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. EMEA, 2006	EMEA/CHMP/BMWP/42832/2005
Guideline on similar biological medicinal products containing monoclonal antibodies	EMA/CHMP/BMWP/403543/2010
Points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis. EMEA, 2003	EMEA/CPMP/EWP/556/95 rev 1 final
Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. EMEA, 2009	CPMP/EWP/4891/03
Guideline on the choice of the non-inferiority margin. EMEA, 2005	EMEA/CPMP/EWP/2158/99
Guideline on the investigation of bioequivalence. EMEA, 2010	CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. EMEA, 2007	CHMP/EWP/89249/2004

During the development of CT-P13 the Applicant sought scientific and procedural advice from the CHMP. The scientific advice procedures covered questions on the pharmaceutical quality, the non-clinical and clinical programme. The scientific advice received by the CHMP was generally taken into consideration and any deviation was discussed by the Applicant.

2.2. Quality aspects

2.2.1. Introduction

Remsima (also referred to as CT-P13) contains the active substance infliximab, which is a chimeric human-murine IgG1 monoclonal antibody that binds with high affinity to both soluble and transmembrane (tm) forms of tumour necrosis factor alpha (TNFα). Infliximab prevents TNFα receptor activation by binding to TNFα, thereby neutralising the biological activity of TNFα.

CT-P13 has been developed as a similar biological medicinal product to the reference medicinal product (RMP) Remicade (infliximab). The formulation development process for Remsima has been designed to replicate the RMP Remicade and both medicinal products are identical with respect to strength, pharmaceutical form, route of administration, composition in excipients.

2.2.2. Active Substance

Like other IgG subclasses, CT-P13 is a glycoprotein with one N-linked glycosylation site (Asn 300) in the CH2 domain of each heavy chain. The detected oligosaccharides are mostly G0F (absence of terminal galactose) and G1F (one terminal galactose) structures. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in heavy and light chain are involved in either intra- or inter-disulphide bonding.

Manufacture

The active substance is manufactured at Celltrion Inc, 13-6 Songdo-dong, Yeonsu-gu, Incheon, 406-840, Republic of Korea.

Development genetics

The Sp2/0-Ag14 cell line was formed by fusing BALB/c spleen cells (from mouse immunised with sheep red blood cells) with the P3X63Ag8 myeloma. Generation of the CT-P13 cell substrate was accomplished using standard cell line transfection and methotrexate amplification protocols for the expression vector. The vector encodes both the heavy and light chains and the dihydrofolate reductase expression system.

Cell banking system

A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed from a pre-MCB and maintained in accordance to current Good Manufacturing Practices and ICH guidelines. An end-of-production cells bank (EPCB) derived from the WCB was also generated with cells used for commercial production of CT-P13.

Procedures followed for the preparation of the MCB, WCB and EPCB were described. An extensive range of tests was performed for their characterisation, in accordance to ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation process

The CT-P13 manufacturing process is initiated using a single vial of the WCB. The cells are expanded to sufficient numbers to seed the production bioreactor. After fixed production duration, the cell culture media is harvested and filtered. The harvested cell culture fluid (HCCF) is then stored until initiation of downstream operations.

Each of the cell expansion steps has been described in sufficient detail. Critical process parameters are justified and appropriate in-process controls are specified for the cell culture steps, including viable cell

density and cell viability. In-process control tests are sufficient to ensure the microbial safety of the product and consistent quality.

Purification process

CT-P13 is purified through a series of chromatographic steps, viral inactivation and nanofiltration steps and ultrafiltration/diafiltration step.

Each step of the purification process has been adequately described, including descriptions of the different buffers used, column regeneration and storage conditions. Process hold steps are detailed and appropriate data to support product intermediate hold times has been provided. The critical process parameters for each process step are justified and appropriate in-process controls, with justified acceptance limits, are specified. In-process control tests are sufficient to ensure the microbial/viral safety of the product, and consistent quality.

Process validation and/or evaluation

Extensive process validation was undertaken for the CT-P13 active substance manufacturing process at Celltrion, Korea.

The validation for the upstream process included several production bioreactors. Evaluation at commercial scale included a bioreactor agitation study and harvest optimisation study.

The downstream process was validated using full scale harvest batches. A qualified scale-down model for the purification process was used to evaluate virus clearance and removal of impurities (host cell proteins (HCP), DNA, leached Protein A and media components) via impurity spiking studies. The validation strategy included demonstration of adequate column cleaning and lack of cross contamination between purification runs. In addition, the hold times for media and buffers used during production were evaluated, along with product intermediate hold steps during production. Reprocessing validation, shipping validation and results from a freeze-thaw study were also covered.

Manufacturing process development

During process development, several changes were made to the manufacturing process to improve product and process consistency. Appropriate product comparability studies have been carried out to demonstrate that the process changes have not impacted on key product quality attributes.

All the changes to the CT-P13 active substance manufacturing process were implemented after production of the batches used in pivotal non-clinical and Phase I/III clinical studies.

Characterisation

An extensive product characterisation exercise was conducted, using a range of state-of-the-art orthogonal methodologies in order to elucidate the primary, secondary and higher order structure, post-translational modifications and associated micro-heterogeneity, glycosylation, charged isoforms, purity and biological activity associated with CT-P13.

Given that CT-P13 was developed as a similar biological medicinal product, an extensive comparability alongside the RMP, Remicade, was undertaken. Data and discussion pertaining to comparability with the RMP are located in section 2.2.4.

A) Elucidation of structure and other characteristics

A1) Physicochemical characterisation

A range of techniques has been employed in order to elucidate the primary structure of CT-P13, these include:

- Amino acid analysis: content analysed by acid hydrolysis, derivatisation, reversed phase high performance liquid chromatography (RP-HPLC) and fluorescence detection.
- Peptide mapping: active substance and finished product were analysed by liquid chromatography mass spectrometry (LC-MS) peptide mapping.
- Analysis of post-translational modifications.
- N-terminal and C-terminal sequencing by peptide mapping in combination with tandem mass spectrometry (MS/MS).
- Heavy and light chain mass was determined by liquid chromatography electrospray ionisation mass spectrometry (LC-ES-MS)

The elucidation of higher order structures included the following assessments:

- Determination of disulphide bond location by native and reduced peptide mapping.
- Determination of the amount of free sulfhydryl groups using Ellman's reagent.
- Secondary structure analysis using Fourier transform infrared spectroscopy (FTIR) and circular dichroism (far UV).
- Tertiary structure analysis using circular dichroism (near UV).
- Differential scanning calorimetry (DSC) to assess the thermal stability and general higher order structure of CT-P13.

In relation to purity/impurity:

- Aggregate content and monomeric purity was determined by size exclusion chromatography (SEC-HPLC) under non-denaturing conditions.
- Determination of electrophoretic mobility and purity was performed using capillary electrophoresis sodium dodecyl sulphate (CE-SDS). Non-reducing conditions were used for determination of levels of intact IgG (H2L2) and any detectable non-assembled antibody species. Reducing CE-SDS was performed for determination of purity.
- In order to characterise the CT-P13 IgG fragments, CT-P13 finished product was assessed by means of SDS polyacrylamide gel electrophoresis (SDS-PAGE). The bands identified were excised and subject to LC-MS analysis.

There are a number of post-translational modifications that have the potential to influence CT-P13 charge heterogeneity, notably C-terminal lysine variability, product deamidation, product oxidation and glycosylation. The CT-P13 charged variants were analysed using isoelectric focusing (IEF), ion exchange chromatography (IEC-HPLC) combined with tryptic peptide mapping (charge isoform distribution) as well as LC-MS peptide mapping (oxidised molecular variants).

Glycosylation:

In order to fully elucidate the sites of glycosylation, as well as the glycan micro-heterogeneity associated with the molecule, a range of state-of-the-art methodologies has been employed, including site-specific glycosylation analysis (LC-MS peptide analysis and oligosaccharide profiling) to determine the range of glycan structures displayed by CT-P13 at Asn300. In addition to this, monosaccharide analysis of neutral and amino sugars has been undertaken and the type/amount of sialic acids capping the glycan structures has been assessed.

- N-linked glycan analysis: LC-MS analysis of the peptides generated during peptide mapping was used

for determination of oligosaccharide structures, attachment sites and distribution. Selected ion chromatograms were used to quantify each oligosaccharide species. The data confirmed Asn300 as the only site of N-glycosylation. As expected for an IgG1 monoclonal antibody, no O-linked glycans were detected.

- Oligosaccharide profiling: to further characterise the glycan micro-heterogeneity associated with this single N-glycosylation site, high-performance anion exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD) was used to resolve and reveal the oligosaccharide structures. The identified structures, G0F, Man5, G1F and G2F are in agreement with the typical oligosaccharide profile of a monoclonal antibody.

- Monosaccharide analysis: determination and quantitation of neutral and amino sugar composition was performed by acid hydrolysis followed by chromatography to separate the monosaccharides.

- Sialic acids were analysed by HPAEC-PAD analysis. Sialic acid was detected in the form of N-glycolylneuraminic acid (NeuGc) in all samples, with no other forms detected.

A2) Biological characterisation

The biological activity of infliximab can be categorised into two parts. The primary mechanism of action involves the TNFα neutralisation by binding to TNFα and inhibition of cell signalling for proliferation. Assays for this include *in vitro* TNFα neutralisation activity, apoptosis, TNFα binding affinity by Surface Plasmon Resonance (SPR) and ELISA, and cell-based TNFα binding affinity assay. The secondary mechanism of action involves the activation of the immune responses which includes antibody-dependent cell cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), FcγR family binding affinity (SPR), FcRn binding affinity (SPR) and C1q binding affinity (ELISA).

B) Variants and impurities

B1) Product-related variants and impurities

- Charged isoforms as determined by IEC-HPLC: the biological activity of all IEC-HPLC peaks was subject to analysis with respect to *in vitro* TNFα neutralisation activity, TNFα binding affinity by ELISA, C1q binding affinity by ELISA, FcγRIIIa binding affinity by SPR and FcRn binding affinity by SPR. The data show that all IEC-HPLC peaks are biologically active.

- Oxidised variants as determined by LC-MS peptide mapping: low levels were detected in active substance and finished product batches. It is considered that these variants have no deleterious effect on the efficacy of the product.

- IgG fragments as determined by CE-SDS (non-reduced and reduced): IgG fragment was investigated for TNFα binding affinity (ELISA) and *in vitro* TNFα neutralisation activity.

- Glycan variants as determined by CE-SDS, peptide mapping LC-MS and HPAEC-PAD: a study was performed to investigate the correlation between glycosylation and Fc function of CT-P13. The presence of Fc glycans influences the binding of IgG to Fc receptors and C1q; in the case of CT-P13, such binding is associated with ADCC and CDC activity, which are secondary mechanisms of action associated with infliximab. This binding ability is affected by Fc glycan variability; therefore the FcγRIIIa and C1q binding affinities were studied using SPR and ELISA methods, respectively, in order to determine the correlation between glycosylation and bioactivity. In particular, the influence of glycan moieties on the Fc domain of IgG bioactivity (FcγRIIIa binding affinity and C1q binding affinity) was studied. The correlation between glycosylation and biological activity was assessed through the modulation of aglycosylation and agalactosylation. The impact of aglycosylation on bioactivity in terms of FcγRIIIa and C1q binding affinity is substantial. Nevertheless, the amount of aglycosylated protein was below the limit of quantitation for all CT-P13 active substance and finished product samples tested to date, therefore the

findings of this aglycosylation study do not hold implications for the efficacy of the CT-P13 finished product. The data also indicate that galactosylation does not influence bioactivity in terms of FcγRIIIa and C1q binding.

- High-molecular weight species as determined by SEC-HPLC: forced degradation data demonstrate that low pH and high temperature result in product aggregation and that the vast majority of product aggregate results from non-covalent forces. The study also showed a correlation between CT-P13 product aggregation and decreased biological activity, as determined by TNFα neutralisation.

B2) Process-related impurities

The process-related impurities associated with CT-P13 include HCP, host cell DNA, rProtein A and media components. Other potential contaminants include bioburden and endotoxins.

Specifications

Batch release results from full-scale batches were presented in the dossier. The results were consistent and within the defined acceptance criteria in place at the time of manufacture. The commercial release specifications have been defined on the basis of process capability and product quality.

The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, quantity, potency and safety (microbial).

All methods have been satisfactorily validated with regard to specificity, accuracy, precision, linearity, and robustness.

Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance to current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

The stability data provided support a 36 month shelf-life for the active substance stored at -40±5°C and a 6 month shelf-life when stored at 5±3°C.

In accordance to EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The CT-P13 finished product is formulated as a white lyophilised powder in a 20 mL Type I borosilicate glass vial with a 20 mm, double vent butyl rubber stopper and a 20 mm aluminium flip-off seal. All components are in compliance with the European Pharmacopoeia.

The finished product is composed of 100 mg CT-P13 active substance, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate, sucrose and polysorbate 80 as excipients. All excipients are of pharmacopoeial grade.

Since the CT-P13 formulation was set identical to that of Remicade, only limited qualitative and quantitative formulation studies have been performed, the purpose of which was to demonstrate the formulation used was adequately robust in terms of product stability and quality and comparable with the RMP.

No overfill is used in CT-P13 finished product manufacture.

The lyophilisate is reconstituted with 10 mL of sterile water for injections to yield a single dose formulation of 10 mg/mL infliximab, at pH 7.2. Each vial is designed to deliver a single dose of 100 mg CT-P13 active substance.

During product development, a total of three finished product manufacturing sites have been used; one site was used for supply of material used in initial non-clinical studies, and two manufacturing sites have been used for supply of clinical material and licensed for commercial supply. However, the manufacturing process for the finished product has not significantly changed as a result of the change in manufacturers, although the scale of finished product manufacture is different at the two sites that will be used for commercial supply. Nonetheless an extensive comparability study has been undertaken which demonstrated that there were no significant differences in the quality of finished product manufactured at these three sites.

Adventitious agents

The non-viral and viral adventitious agents safety evaluation is discussed in section 2.2.4.

Manufacture of the product

The finished product manufacturing process comprises an initial dilution of bulk active substance followed by terminal sterile filtration prior to filling and lyophilisation. Finally, the vials are stoppered, sealed and capped, 100% inspected then labelled and packaged into the secondary containers.

The manufacturing process at both sites that will be used for commercial supply has been fully validated at their respective commercial scales of manufacture. The validation studies covered preparation of formulation buffer, final formulation (dilution) of the bulk active substance, sterile filtration, demonstration of aseptic processing via media fill studies, the lyophilisation process and finally stoppering, capping and crimping. In addition, hold times of buffers and product intermediates were validated. The results demonstrated that the manufacturing process at both sites is robust and consistently yields product capable of meeting pre-defined quality characteristics.

Product specification

Batch release results from full scale batches were presented in the dossier. The results were consistent and within the defined acceptance criteria in place at the time of manufacture. The commercial release specifications for the finished product have been defined on the basis of process capability and product quality.

The control tests proposed for the finished product are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, quantity, potency and safety (microbial), as well as pharmacopoeial tests required specifically for parenteral products to be administered by infusion.

All methods have been satisfactorily validated with regard to specificity, accuracy, precision, linearity, and robustness.

Stability of the product

Real-time and accelerated stability studies were initiated in accordance to ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. On the basis of the data provided, the approvable shelf-life for the finished product is 36 months at 5 ± 3°C. In terms of in-use shelf-life, the available data show that the reconstituted finished product is stable for up to 48 hours when stored at 5 ± 3°C or 30 ± 2°C/65 ± 5% RH. If not used immediately, in-use storage times

and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C.

In accordance to EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Comparability Exercise for Finished Medicinal Product

A comprehensive and state-of-the art comparability exercise was performed for the proposed CT-P13 biosimilar product with the RMP Remicade. The Applicant has used multiple batches of CT-P13 finished product and Remicade for each analysis. All batches of Remicade were sourced in the EU. In many of the analytical evaluations, CT-P13 active substance was also used; this has a similar formulation (in liquid form) to the finished product. Infliximab was not extracted from the RMP since the formulation does not interfere with the analytical methods used.

An overview of the program of comparability testing that has been undertaken is provided in Table 1 and Table 2. Comparability with the RMP is discussed in section 2.2.4.

Table 1 Summary of Physicochemical Test Methods for Comparability of CT-P13 Active Substance and Finished Product with Remicade

Test Method	Purpose	Drug Substance Tested	Drug Product Tested	RMP Tested
Primary Structure				
Amino Acid Analysis	Determination of amino acid composition	–	√	√
Peptide Mapping (LC-MS) in combination with MS/MS	Comparison of peptide coverage and chemical modifications	√	√	√
Peptide mapping (HPLC)	Comparison of tryptic peptide map by visual inspection	√	√	√
N-terminal Sequencing	Comparison of N-terminal sequences	√	√	√
C-terminal Sequencing	Comparison of C-terminal sequences	√	√	√
Reduced Mass	Comparison of molecular weights by mass spectrometry	√	√	√
Test Method	**Purpose**	**Drug Substance Tested**	**Drug Product Tested**	**RMP Tested**
Higher Order Structure				
Disulphide Bonds	Comparison of disulphide bonds location	√	√	√
Free Thiol Analysis	Comparison of the amount of free sulph-hydryl groups	√	√	√
FTIR	Comparison of secondary structures	√	√	√
CD	Comparison of secondary structure	√	√	√
DSC	Comparison of thermal stability and determination of thermal transition temperatures	√	√	√
Purity/ Impurity				
SEC-HPLC	Comparison of aggregate content and monomeric purity	√	√	√
CE-SDS (Reduced/Non-Reduced)	Comparison of electrophoretic mobility and purity under non-reducing and reducing conditions	√	√	√

Test Method	Purpose	Drug Substance Tested	Drug Product Tested	RMP Tested
Charged Isoforms				
IEF	Comparison of isoelectric point(s)	√	√	√
IEC-HPLC	Comparison of charge variant distribution	√	√	√
Glycosylation				
Sialic Acid Analysis	Comparison of sialic acid content	√	√	√
Monosaccharide Analysis	Comparison of neutral and amino sugar composition	√	√	√
Oligosaccharide Profiling	Comparison of glycosylation pattern (ex. G0F, G1F, G2F)	√	√	√
N-linked Glycan Analysis	Comparison of oligosaccharide structures, attachment sites and distribution	√	√	√
Content				
Protein Concentration (UV_{280})	Comparison of protein concentration	–	√	√
Product Specific ELISA	Comparison of infliximab API content	√	√	√

Table 2 Summary of Studies Comparing Biological Activity between Remsima and Remicade

Test Method	Key Findings
Fc Receptor related	
Comparative binding to Fcγ receptors: FcγRI, FcγRIIa, FcγRIIb, and FcRn using Surface Plasmon Resonance [SPR]	The relative binding affinities of Remsima and Remicade to Fcγ receptors (FcγRI, FcγRIIa, FcγRIIb and FcRn) were comparable.
Comparative binding to Fcγ receptors: FcγRIIIa (V and F hemizygotes) and FcγRIIIb using SPR	Differences in the relative binding affinity of Remsima and Remicade FcγRIIIa and FcγRIIIb were detected; reduced binding to FcγRIIIa (V and F hemizygotes) and FcγRIIIb was detected in Remsima lots.
Comparative binding to Fcγ receptors: *Ex vivo* assay using NK cells and neutrophils to assess FcγRIIIa and FcγRIIIb binding, respectively	There was a difference in mean relative binding affinities to isolated NK cells of healthy donors and Crohn's disease (CD) patients (between Remsima and Remicade, which was shown to be FcγRIII genotype dependent (V/V and V/F genotypes, respectively). No differences were shown with F/F genotype. In the presence of diluted CD patient serum all differences in binding for Remsima and Remicade lots were abrogated.
	The mean relative binding affinities of Remsima and Remicade to isolated neutrophils (*ex vivo*) from a healthy donor or CD patient were shown to be comparable.

Test Method		Key Findings
F(ab')2 related		
Comparative binding of Remsima and Remicade to hTNFα using ELISA		The relative binding affinities of Remsima and Remicade were shown to be comparable. Remsima and Remicade demonstrated comparable binding activity to both monomeric and trimeric hTNFα.
Comparative binding of Remsima and Remicade to hTNFα using Surface Plasmon Resonance [SPR]		Similar equilibrium binding affinities (K_D) toward the intact trimeric form of hTNFα. The binding affinity of Remsima and Remicade to monomeric and trimeric hTNFα was comparable. The relative binding affinities of Remsima and Remicade were shown to be comparable for hTNFα. Remsima and Remicade demonstrated comparable binding to both monomeric and trimeric hTNFα.
Comparative transmembrane (tm) hTNFα binding affinity of Remsima and Remicade using cell-based ELISA		The relative binding affinities of Remsima and Remicade were shown to be comparable.
The human TNFβ binding specificities of Remsima and Remicade		Neither Remsima nor Remicade had binding affinity for hTNFβ.
Human tissue cross-reactivity of Remsima and Remicade using immunohistochemistry		The tissue cross-reactivity of biotinylated Remsima and biotinylated Remicade were shown to be comparable using a panel of human tissues.
Comparative TNFα binding affinity from different species of Remsima and Remicade using SPR		For Remsima and Remicade, neither product displayed binding affinity for mouse, rat, canine, porcine, or rhesus monkey TNFα.
Comparative hTNFα neutralisation assay of Remsima and Remicade		The neutralising activities of Remsima and Remicade on a TNFα sensitive cell line were shown to be dose dependent and comparable and within ≤15% of assay variance.
Comparative apoptosis of Remsima and Remicade		The apoptotic effects by reverse signalling through tmhTNFα for Remsima and Remicade were comparable. No statistically significant differences were detected at any time point.
Comparative Reverse signalling		Blockade of pro-inflammatory cytokine production by reverse signalling through tmhTNFα for Remsima and Remicade were comparable, using peripheral mononuclear blood cells (PBMC) from either healthy donors or CD patients.
Effect of blocking soluble TNFα in *in vitro* IBD model	Suppression of cytokine secretion in epithelial cell line by blocking soluble TNFα	Suppression of pro-inflammatory cytokine (IL-6 and IL-8) secretion from co-stimulated epithelial cell line was shown to be comparable and dose dependent for Remsima and Remicade; no statistical difference in pro-inflammatory cytokines suppression was found.
	Suppression of apoptosis in epithelial cell line cells by blocking soluble TNFα	Suppression of epithelial cell line apoptosis was shown to be comparable for Remsima and Remicade.

Test Method		Key Findings
Fc-F(ab')2 related		
Comparative C1q binding affinity of Remsima and Remicade using ELISA		The relative binding affinities of Remsima and Remicade were shown to be comparable.
Comparative complement-dependent cytotoxicity (CDC) of Remsima and Remicade		CDC effects of Remsima and Remicade against tmhTNFα-Jurkat cells by lysis were comparable. No statistically significant differences were detected in relative CDC activity.
Comparative antibody-dependent cell-mediated cytotoxicity (ADCC) of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and human PBMC as effector cells		Remsima and Remicade had comparable ADCC activity and no statistically significant differences were detected.
Comparative ADCC of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and NK cells from healthy donor as effector cells		Comparable ADCC for Remsima and Remicade when NK cells from a healthy donor (genotype V/F) were used as effector cells.
Evaluation of Regulatory Macrophage Function	Suppression of T cell proliferation by induced regulatory macrophages in mixed lymphocyte reaction (MLR) assay	Inhibition of T cell proliferation of PBMCs from healthy donors and CD patients was shown to be comparable and dose dependent for Remsima and Remicade.
	Quantitation of the induced regulatory macrophages by FACS analysis	Induction of regulatory macrophages in a 2-way allogenenic MLR using FcγRIIIa genotype matched PBMCs, from either healthy donors or CD patients, was shown to be comparable for Remsima and Remicade.
	Induced regulatory macrophage-mediated wound healing of colorectal epithelium cells	Promotion of *in vitro* wound healing of colorectal epithelial cells by regulatory macrophages from healthy donors and CD patients (induced by Remsima or Remicade) in the MLR assay was comparable.
Comparison of ADCC activity between Remsima and Remicade using transfected Jurkat cells as target cells and either PBMCs or NK cells from CD patients as effector cells		No differences in ADCC activity were detected using PBMC from CD patients (V/F or F/F genotype). Differences in ADCC with Remsima and Remicade were seen when NK cells from CD patients were used as effector cells. Effect was FcγRIIIa genotype specific; differences were observed with V/V and V/F, but not F/F genotypes.
Comparison of ADCC effect between Remsima and Remicade using transfected Jurkat cells as target cells and whole blood from healthy donor or CD patients as effector cells		No differences in ADCC were seen between various batches of Remsima and Remicade.
Comparison of ADCC between Remsima and Remicade using LPS-stimulated monocytes from healthy donor or CD patient as target cells and PBMC as effector cells		No ADCC activity was seen with Remsima and Remicade when PBMCs from a healthy donor (V/F) or a CD patient (V/F) were used as effector cells and LPS-stimulated monocytes were used as target cells.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

- ***Active substance***

The CT-P13 active substance manufacturing process is controlled by process parameters (input variables) as well as by in-process tests (output variables). Based on their influence on the identified CQAs, the process parameters have been divided into critical (CPPs) and non-critical (non-CPPs). The establishment of the CQAs and the risk assessment to support the assignment of criticality to process

parameters were described. Further information and improvements were provided in order to achieve a satisfactorily controlled active substance manufacturing process. The proposed CPP acceptance limits/ranges have been updated based on historical batch data and characterisation and are acceptable. The control of the active substance manufacturing process was considered acceptable, following a request by the CHMP for clarification of the strategy.

The Applicant has described the generation of the cell line, including details of the plasmid, manufacture of the transfected cells and selection of the production clone. Extensive testing and characterisation were performed on the MCB, which is satisfactory. Less characterisation has been performed for the current WCB, which is acceptable. Details for establishing future WCBs have also been provided.

Cells at the limit of *in vitro* cell age were characterised from the EPCB and acceptable testing results for the EPCB are provided. Retrovirus particles have been identified, as expected for this cell line. Genetic stability testing for the EPCB compared with the MCB indicated a significant reduction in gene copy number, but although this affects productivity, the quality of CT-P13 from the EPCB was shown to be acceptable. Evaluation using a scale-down model showed similar growth profiles from the MCB to the EPCB, but clear differences in the cumulative product titre were demonstrated. Product quality was examined for differences in impurities (SEC-HPLC and CE-SDS), oligosaccharide profile and charge variants (IEC-HPLC), in addition to primary structure (peptide mapping), secondary structure (differential scanning calorimetry) and *in vitro* biological activity (TNFα neutralisation assay). Apparent differences observed in IEC-HPLC and the oligosaccharide profile in the *in vitro* cell age limit cells and EPCB were shown to be due to the different preparation methods for these samples, resolving initial concerns. The passage number for the "*in vitro* cell age at harvest of routine production" has been clarified and related to numbering in process validation data and data from batches at the production scale to date.

On the whole, the Applicant has demonstrated control of the raw materials used during the manufacture of CT-P13. For the cell culture medium components, acceptance criteria have been introduced for endotoxin, microbial limits, osmolality and pH, which are satisfactory.

Extensive process validation has been undertaken for the CT-P13 active substance manufacturing process. The validation for the upstream process and downstream process showed that all the parameters were within the acceptance criteria and demonstrated that the process was validated. Evaluation of the manufacturing process included a bioreactor agitation study and harvest optimisation study (centrifuge feed flow rate). A qualified scale-down model for the purification process was used to evaluate virus clearance and removal of impurities (HCP, DNA, leached Protein A and media components) in spiking studies. It is noted that aged resin was used for the virus clearance study. All these impurities showed clearance in the studies, except for Protein A. The effective clearance of impurities was confirmed using data from the full scale manufacturing process. A resin lifetime study was also performed at small scale and the results have been confirmed at the manufacturing process scale. Cleaning efficiency for the chromatography columns was demonstrated and is monitored at intervals during the production process. The hold times for media and buffers used during production have been evaluated, along with the hold steps during production; the cumulative hold times have been specified and justified. Reprocessing validation (virus filtration and final filtration), shipping validation and results from a freeze-thaw study have all been provided.

Overall the information from the validation runs is appropriately detailed and demonstrates consistent performance of the manufacturing process when run at target. After completion of process validation, some of the active substance specifications and in-process control acceptance criteria were tightened based on re-evaluation of batch data accumulated, in order to monitor and evaluate process performance and product quality attributes more efficiently. Clarification has been provided for the number of viral filtration reprocessing cycles permitted during the manufacturing process and the

number of times the reprocessing step at the final filtration and filling stage is allowed.

During process development, several relatively minor changes were made to the manufacturing process. The essential elements of the CT-P13 active substance manufacturing process, including the production scale, the methods of chromatographic separation and the number and sequence of processing steps, were retained throughout process development.

Comparability to support manufacturing changes made during has been demonstrated using batch analysis and additional characterisation. Comparison of primary structure and higher order structures, micro-heterogeneity, post-translational forms, purity profile and biological activity of the active substance were used to demonstrate comparability. Some batch-to-batch variability in N-glycans was detected by two LC-MS methods (quadrupole time-of-flight and liquid chromatography quadrupole MS), but no clear trend was observed before and after the changes. There were also differences in the quantitation of the Man5, G1F and G2F between these two methods; this was considered to be a difference in the accuracy and sensitivity between the methods. Small differences in oligosaccharide profiling (relative %) were observed before and after changes, but these were not reflected in the MS results. Analysis of pre- and post-change batches by circular dichroism showed no significant difference in the higher order structure. TNFα binding affinity (by ELISA and SPR) was comparable and FcγRIIIa binding affinity (SPR) was also comparable pre- and post-change. C1q binding appeared slightly lower in pre-change batches, but when these were re-tested with additional replicates, there was no difference observed.

Extensive characterisation has been performed for CT-P13 using both active substance and finished product manufactured using the proposed commercial process. These batches of finished product were also used in Phase I/III clinical studies and in stability/comparability/process validation studies. The primary structure of CT-P13 was determined using amino acid analysis, peptide mapping (by LC-MS, using trypsin and either Lys-C or Asp-N enzymes), N-terminal sequencing, C-terminal sequencing and mass spectrometry. The higher order structure of CT-P13 was determined by assessment of the position of disulphide bonds (native and reduced peptide mapping) and free thiol analysis; secondary structure analysis using FTIR spectroscopy and circular dichroism (far UV); tertiary structure analysis using circular dichroism (near UV); as well as DSC to assess the thermal stability of the molecule. These studies revealed the expected results for a monoclonal antibody and confirmed the expected primary sequence for infliximab.

In terms of purities/impurities, CT-P13 was shown to be predominantly monomeric, with only low levels of high molecular weight aggregates detected by SEC-HPLC. Forced degradation studies showed that low pH and high temperature triggered non-covalent aggregation, which results in decreased biological activity as determined using the *in vitro* TNFα neutralisation assay. The level of aggregates is controlled in the active substance and finished product via the monomer content. Extensive analysis by SDS-PAGE (non-reducing) showed that the majority of CT-P13 comprised H2L2. The biological activity of the IgG fragment was analysed for TNFα binding affinity (by ELISA) and potency (*in vitro* TNFα neutralisation assay), showing no measurable differences between CT-P13 and samples with increased levels of IgG fragment in either of these assays. Intact IgG is controlled in CT-P13 (purity by CE-SDS, non-reduced) and the specification was tightened based on the levels of intact IgG in the batches of finished product used in the clinical trials. The specification will also apply at the end of shelf-life. Purity was also determined by CE-SDS (reduced) with the limit employed at active substance and finished product release.

The C-terminal lysine variability, common in IgG molecules, was confirmed by amino acid analysis, peptide mapping and C-terminal sequencing. The proportion of molecules without C-terminal lysine (K0) represented the most commonly occurring fractions identified by IEC-HPLC, in agreement with the LC-ES-MS data.

The Applicant has applied orthogonal methods in order to fully characterise the charged isoforms in CT-P13, detected by IEF or identified by IEC-HPLC (cation exchange chromatography). Structural analysis for each of the fractionated peaks showed multiple molecular variants which were assigned to differences in C-terminal lysine, site-specific deamidation and charged glycan species. The charged isoforms were identified as product-related substances, based on biological characterisation of the fractionated peaks, compared with the reference standard. Analysis showed comparable relative activity in the *in vitro* TNFα neutralisation activity, TNFα binding affinity by ELISA, FcγRIIIa binding affinity by SPR and FcRn binding affinity by SPR, with slightly lower activity determined using the C1q binding affinity by ELISA. In the forced degradation studies, it was revealed that CT-P13 deamidation occurs more rapidly at high pH and high temperature, with corresponding changes to the IEC-HPLC peak ratio due to an increase in acidic forms. TNFα neutralising activity was assessed for samples subject to forced degradation; at pH 10.5 (5°C for 7 days) the amount of deamidated species was seen to increase very slightly and was associated with a marginal decrease in TNFα neutralising activity, within the variability of the cell-based assay. It is accepted that these charged isoforms are classified as product-related substances, although they are still controlled in the routine Quality Control (QC) at active substance and finished product release. This approach has been followed to ensure that the commercial CT-P13 finished product will be comparable to the CT-P13 finished product qualified during Phase III clinical trials.

Glycosylation was also analysed using several analytical methods. Site-specific glycosylation analysis (by LC-MS peptide analysis and oligosaccharide profiling) was used to determine the range of structures at the single N-linked site at Asn300. No O-linked glycosylation was identified, as expected for IgG. CT-P13 active substance and finished product contain mostly G0F and G1F glycans, which are the typical biantennary glycans found on IgG with no galactose (G0), or one galactose and a core fucose (G1F). A range of minor species were also identified (Man5, G0F minus GlcNAc, G0 and G2F) and there were two charged glycans, G1F1NeuGc and G2F1NeuGc. Analysis of isolated glycans confirmed these results on the whole, although higher levels of G1F glycans were detected using HPAEC-PAD. There also appeared to be lower levels of sialylated glycans in the finished product samples by the glycan analysis, although this was not confirmed by the later sialic acid analysis, which showed similar levels of N-glycolyl neuraminic acid in CT-P13 active substance and finished product samples. The levels of aglycosylation detected in CT-P13 active substance or finished product were below the limits of detection.

The biological activity of infliximab can be categorised into two parts. The primary mechanism of action involves the TNFα neutralisation by binding to TNFα and inhibition of cell signalling for proliferation, which was studied by *in vitro* TNFα neutralisation activity, apoptosis, TNFα binding affinity (SPR or ELISA) and cell-based TNFα binding affinity. The secondary mechanism of action involves the activation of the immune responses which includes ADCC, complement-dependent cytotoxicity (CDC), FcγR family binding affinity (SPR), FcRn binding affinity (SPR) and C1q binding affinity (ELISA). For the analysis of biological activities, CT-P13 in-house reference materials effective at the time of testing were used.

The correlation between glycosylation and Fc function of CT-P13 has been investigated. The presence of Fc glycans influences the binding of IgG to Fc receptors and C1q; in the case of CT-P13, such binding is associated with ADCC and CDC activity, which are secondary mechanisms of action associated with infliximab. This binding ability is affected by Fc glycan variability; therefore the FcγRIIIa binding affinity (SPR) and C1q binding affinity (ELISA) were studied in order to determine the correlation between glycosylation and bioactivity. The correlation between glycosylation and biological activity was assessed through the modulation of aglycosylation in CT-P13. The level of aglycosylated CT-P13 is significantly lower than the level identified to influence FcγRIIIa binding affinity, therefore this was not considered to be an issue. There was no direct correlation observed between terminal galactose and biological activity; different levels of agalactosylation did not impact FcγRIIIa binding affinity or C1q binding affinity.

Consistency of glycosylation can be affected by fermentation parameters and factors such as

fucosylation are known to influence the Fc function in antibodies. Glycosylation needs to be controlled during the manufacturing process and the Applicant has introduced specifications for the glycosylation in CT-P13 active substance.

Very low levels of oxidised species were detected in CT-P13 active substance or finished product batches (peptide mapping with LC-MS) following storage at 5 ± 3°C for 16 and 10 months, and even following storage of finished product under stress conditions (40 ± 2°C/75 ± 5% RH) for 9 months. However, it is noted that storage of the active substance at 25 ± 2°C/60 ± 5% RH for 16 months did result in significant product oxidation. A forced degradation study showed that a substantial increase in product oxidation did not have a substantial impact on biological activity (*in vitro* TNFα neutralisation assay), with any differences observed within the variability of the assay. Oxidation is not expected to have a deleterious effect on the efficacy of the finished product and therefore oxidised molecular variants are classified as product-related substances. As such, oxidised species will not be assessed during routine QC of the CT-P13 active substance or finished product at release or in stability studies. This is accepted.

Process-related impurities were efficiently cleared during the purification process, which was demonstrated using a combination of spiking studies and results from the process validation and historical batches. In addition, limits were set for HCP, host cell DNA and residual rProtein A in the active substance batch release testing.

The Applicant has validated the analytical methods using CT-P13 active substance. In some cases, addendum studies were performed using these same assays but with additional validation parameters or use of specific impurities/degraded samples in order to complete the validation. The assay validation is satisfactory.

The proposed active substance specification includes general controls (clarity, colour, visible particles, pH), as well as control testing for safety (endotoxin, bioburden), identity (IEF, IEC-HPLC), purity/impurity (IEC-HPLC, reduced and non-reduced CE-SDS, SEC-HPLC, HCP, DNA, residual protein A), content and potency. The test items are in line with the requirements for the active substance in Ph. Eur. 2031, as well as with relevant guidelines. The Applicant has provided a detailed justification for the active substance specifications, with the same acceptance criteria at active substance release and at end-of-shelf-life, to ensure that the CT-P13 active substance is stable during storage. The exception to end-of-shelf-life specifications is the omission of tests for process-related impurities such as HCP, host cell DNA and residual rProtein A, as well as identity by means of IEC-HPLC, which is acceptable. On the whole, the majority of acceptance criteria in the specifications are based on the batch data mean values ± 3SD, which takes into account the batch results and allows for assay variability. The Applicant has re-evaluated the acceptance criteria for purity by IEC-HPLC and introduced additional limits, while also tightening the limit for non-reducing CE-SDS based on batch data. The endotoxin limit is justified based both on batch data and the calculated maximum allowable dose given in Ph. Eur. for parenteral products (10 IU/mL), which is acceptable. The residual DNA limits are also justified based on batch data and this is well below the calculated maximum allowable dose given in Ph. Eur. (10 ng/dose), which is acceptable. The limits proposed for residual HCP were tightened to bring these in line with the batch data. The initial proposed limits for residual rProtein A were reduced based on batch data, since no real clearance of this contaminant was demonstrated in spiking studies.

Revision of the proposed active substance specifications for glycosylation was made following a request from CHMP, with inclusion of Man5 in the afucosylated glycan specification of CT-P13 active substance (G0+Man5). Proposed acceptance criteria were tightened for fucosylated glycans G0F+G1F+G2F (and specifications were included for charged glycans SA1+SA2 in line with batch data.

It is noted that the current and superseded CT-P13 reference standards used in the potency assay were qualified against Remicade with respect to *in vitro* bioactivity, and both reference standards employed to date are closely matched to the reference product in terms of *in vitro* bioactivity. The Remicade

reference standard was prepared by combining multiple batches of Remicade; this was used to establish the CT-P13 reference standard. The information regarding CT-P13 reference standard annual re-qualification, introduction of working reference standard and introduction of a new primary reference standard (in the future) are acceptable, except for use of a reagent grade TNFα to calibrate the CT-P13 reference standard. Following a request from the CHMP, an International Standard for TNFα will be used to calibrate future batches of reference standard/working reference standard, in order to demonstrate that there is no drift in the potency of CT-P13.

The container closure system has been demonstrated to be suitable for its intended use for the active substance.

The Applicant has provided stability data for batches tested at both the proposed storage temperatures and under accelerated conditions (25 ± 2°C/ 60 ± 5% RH). The data demonstrate that IEC-HPLC, CE-SDS (reduced and non-reduced), SEC-HPLC and the *in vitro* bioactivity assay are all stability-indicating assays. The data supports the claimed shelf-life of 6 months at 5 ± 3°C for the active substance. The proposed shelf-life for CT-P13 active substance stored at -40 ± 5°C is 36 months. The stability data indicate that CT-P13 is photo-sensitive and the Applicant has committed to store the active substance away from sources of light, both during storage and during shipment (in a freezer or refrigerator).

- ***Finished product***

The Applicant has used the same pharmaceutical form and formulation throughout development. The proposed commercial CT-P13 finished product formulation is identical to the one which has been clinically qualified and is the same as Remicade. Formulation optimisation studies have been undertaken, as recommended in EMEA/CHMP/BWP/49348/2005 Guideline. Similar results were obtained for stability studies performed using Remicade and the rate of degradation of the two products can be considered comparable.

The CT-P13 finished product manufacturing process has not been changed significantly throughout development; the unit operations are identical, the process parameters are similar and most changes are related to scale-up and minor adaptations to the process at the different facilities. Comparability programmes were undertaken to demonstrate comparability between finished products manufactured at the two different facilities. Slightly higher residual moisture levels were observed between comparability batches. Although these levels are both below the specification, these differences were investigated and shown to be related to the equipment used in preparation of the samples for analysis, not due to any differences in the lyophilisation at these facilities. There were also higher levels of sub-visible particles in finished product from one of the facilities, although these were variable and remained within the Ph. Eur. specification.

The manufacturing process has been validated and can consistently produce CT-P13 finished product of the required quality. Clarification of in-process hold times and filtration contact times has been provided. Two CQAs have been determined for the finished product manufacturing process. CPPs that have impact on the CQA have been identified. Historical data for the in-process controls from both facilities is presented to support the control parameters. The control strategy of finished product manufacturing process has been further clarified and the present strategy is supported by process characterisation data, validation and commercial scale manufacturing experience. All the excipients used in the formulation of CT-P13 finished product comply with compendial requirements.

The analytical methods used for finished product release were originally validated at Celltrion for control of both active substance and finished product. Following the original method validations, further verifications/qualifications were conducted in order to transfer the analytical procedures to the EU release testing site. The inter-laboratory comparability studies initially raised some concern with regard

to the differences in assay performance, but analysis of further batches at both sites provided assurance of the potency assay performance at these two facilities.

The justifications for the specifications are accepted, including the reconstitution time which has been tightened based on batch data. In addition, in line with the active substance specification and considering that no significant trend of decreased purity during real-temperature stability studies are seen, the acceptance limits for purity by IEC-HPLC and by non-reducing CE-SDS were revised to reflect manufacturing capacity, as well as the purity/impurity profile of the clinical batches.

The Applicant has made a reasonable case for exclusion of FcγR binding and the amount of oxidised molecular variants; these omissions from the specifications are accepted. The Applicant has made a case for not introducing a specification for the glycosylation of CT-P13 finished product, based on analysis of glycans present in batches of active substance and finished product. No differences were observed, particularly in parameters which may be affected by the lyophilisation, such as sialylation. Since the glycosylation will be controlled as part of the active substance specification, there is no need for further specifications at the finished product level.

The container closure system has been demonstrated to be suitable for its intended use for CT-P13 finished product. Details of the lyophilisation, capping and crimping hold times have been given for the finished product manufacturing sites. Shipping details under controlled conditions have also been provided.

All stability studies for CT-P13 finished product have been designed in compliance with ICH Q5C guideline. One storage condition is proposed for the CT-P13 finished product (5 ± 3°C), with long-term (real-time/ real-condition) stability testing performed at 5 ± 3°C. In addition, accelerated stability at 25 ± 2°C/ 60 ± 5% RH and stressed stability at 40 ± 2°C/75 ± 5% RH have been conducted. All finished product batches entered into the stability studies were stored in an identical container closure system to that proposed for commercial supply of the CT-P13 finished product.

The Applicant proposes a shelf-life of 36 months when stored at 2-8°C and has provided stability data generated under real time/real temperature conditions to support this shelf-life.

The results of the accelerated stability studies demonstrate that there was no change in the quality of the CT-P13 finished product during storage. No trend was observed for the finished product up to and including the 6 month testing time point, with the exception of the amount of intact IgG molecule (as determined by CE-SDS non-reduced). All batches remained within the proposed commercial acceptance criteria under accelerated conditions.

Stressed stability studies (40 ± 2°C/75 ± 5% RH) were performed and no change was observed in the quality of the CT-P13 finished product during the 3 months of storage. For stability-indicating parameters, no data trend for finished product was noted, with the exception of the amount of intact IgG molecule (as determined by CE-SDS non-reduced). Nevertheless, all batches remained within the proposed commercial acceptance criterion.

In order to understand product stability following reconstitution and dilution, an in-use stability study has also been conducted at two storage conditions: 5 ± 3°C and 30 ± 2°C/65 ± 5% RH, with time points at 0, 24 and 48 hours. The results demonstrate that there was no significant change in the quality of the CT-P13 finished product during the 48-hour period when stored at either temperature. A general trend of an increase in the amount of sub-visible particles was observed over the course of the study for some (but not all) batches; nevertheless, all batches remained within the acceptance criterion up to and including the final testing time point. An additional infusion bag study was performed to evaluate the sub-visible particles, which confirmed that the levels were variable under all conditions tested (5±3°C and 30±2°C/65±5% RH) for 6 batches of CT-P13 at either 3mg/kg or 5mg/kg, but all these remained below the Ph. Eur. limits. The available data shows that the reconstituted finished product prepared as

a dilution for infusion is stable for up to 48 hours when stored at 5 ± 3°C (refrigerated) or 30 ± 2°C/65 ± 5% RH (room temperature). From a microbiological point of view, the product should be used as soon as possible but within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C.

Given that CT-P13 has been developed as a biosimilar medicinal product, stability testing has also been performed using Remicade. Specifically, batches of Remicade have been assessed following storage at various conditions (long-term, accelerated, stressed, in-use upon reconstitution and dilution for infusion); all Remicade batches used for stability testing were stored in the product's native container closure. For the 5 ± 3°C real-time/real-condition storage condition, the available data demonstrate that CT-P13 finished product is comparable to Remicade, since there was no change in the quality of the CT-P13 finished product or Remicade during long-term storage at 5 ± 3°C for the duration of testing (24 months). The protein content for the tested Remicade batches fell below the proposed commercial CT-P13 end-of-shelf-life specification at the 12 months testing time point; this was attributed to the fact that the Remicade batches in the stability study were 'older' than the CT-P13 batches at the time the study was initiated. For accelerated and stress stability testing, it was demonstrated that CT-P13 and Remicade have a comparable degradation profile.

- ***Adventitious Agents***

Non-viral adventitious agents

All animal-derived raw materials used for the production of CT-P13 have been evaluated in relation to the risk of introducing transmissible spongiform encephalopathies (TSE) agents to the product, in accordance with the EMEA/410/01 Rev. 3 Note for Guidance. It was demonstrated that the TSE risk associated with raw materials used during the manufacture of CT-P13 and the development of the production cell line is highly unlikely.

The safety of CT-P13 with regard to adventitious microbial, mycoplasma and fungal agents is considered assured. There are appropriate control systems in place with respect to raw materials and in-house prepared buffers. The in-process testing strategy employed throughout the manufacturing process monitors and controls microbial contamination.

Mycoplasma and microbial bioburden are controlled during manufacture through use of a sanitary and/or aseptic process design. In-process control testing of intermediates for bioburden and endotoxin is also routinely carried out to ensure microbial safety throughout manufacture. Bioburden, sterility (finished product only) and endotoxin are included in the routine active substance and product release strategies which ensure only materials of suitable quality with respect to microbial safety are released for further processing or for commercial supply.

MCB and WCB characterisation included a test for mycoplasma which was negative; the EPCB was also tested and no contamination of mycoplasma was observed. The manufacturing process has intermediate product testing for this potential contaminant, and no positive results have been observed.

Viral adventitious agents

The safety of CT-P13 with regard to adventitious viral agents is assured through the quality control systems in place and validation of the downstream purification process with respect to viral clearance. There are appropriate systems in place in relation to the source, receipt and acceptance of raw materials of biological origin that may pose a contamination risk. No raw materials of animal origin are used during the cell culture process, so there is minimal risk for the introduction of adventitious viral agents in the CT-P13 manufacturing process via this route. Viral agents are likely to be detected through the *in vitro*

adventitious virus testing performed on unprocessed bulk during routine manufacturing; results on unprocessed bulk manufactured at commercial scale, and the *in-vitro* adventitious virus testing that has been carried out on a routine basis for unprocessed bulk of all the batches produced indicate that adventitious agents are not introduced or detected in CT-P13. However, based on the characterisation of cell banks (MCB and EPCB), it is known that type A and type C retroviral particles could be present in the fermentation harvest and the CT-P13 purification process is validated to demonstrate clearance of this potential impurity in the final product. All other virus screening tests used for cell line characterisation were negative.

For the endogenous retroviruses, the presence of these particles is expected given the observation of retrovirus-like particles in the MCB and EPCB. However, the co-cultivation assay using *Mus dunni* cells demonstrated that no infectious retrovirus-like particles could be detected in unprocessed bulk that was tested. In addition active substance batches have also been tested for evidence of retrovirus infectivity (using the co-cultivation assay using *Mus dunni* cells) and all these were negative. As such, there is evidence that no infectious virus particles are present in active substance.

The CT-P13 purification process steps validated for virus clearance were the low-pH treatment, the nanofiltration and two orthogonal chromatographic unit operations. Viral clearance of CT-P13 was evaluated in scaled-down studies by spiking a relevant virus and non-specific model viruses into process intermediates obtained from active substance batches. Reduced scale models of the chromatography steps and the low-pH treatment and viral filtration steps were used to evaluate clearance of A-MuLV, MVM, pseudorabies virus (PrV), and reovirus-3 (Reo-3). For the reduced scale viral clearance studies, process parameters that were considered likely to influence the viral clearance/inactivation were run using worst-case conditions, or evaluated at the extremes of the defined operating ranges. A-MuLV was studied because it represents the retroviruses present in the host cell line. The non-specific model viruses were chosen in accordance with ICH Q5A (R1) to represent a combination of RNA and DNA viruses, enveloped and non-enveloped viruses, and a wide range of virus families of variable particle size and chemical resistance.

A-MuLV was used as a relevant virus for the retroviruses particles present in Sp2/0 cell lines. Considering average retrovirus-like particles present in unprocessed bulk, a minimum of clearance is required in the downstream process to achieve ≤1 particle per million doses. The virus clearance study has demonstrated sufficient log reduction for A-MuLV through the downstream manufacturing process, demonstrating that the CT-P13 manufacturing process has an adequate safety margin for the retrovirus removal.

Viral clearance on new or aged resin for MVM, PrV or Reo-3 was also considered satisfactory. The virus carry-over study also demonstrated that the column cleaning and regeneration processes for two chromatography resins are effective and capable of removing residual virus if applicable.

Based on all the data provided, it can be concluded that the viral safety of CT-P13 finished product is assured.

- ***Comparability with the Reference Medicinal Product***

A comprehensive and state-of-the-art comparability exercise has been performed for the proposed CT-P13 biosimilar product with the RMP Remicade. The Applicant has used multiple batches of CT-P13 finished product and Remicade for each analysis. All batches of Remicade were sourced in the EU. In many of the analytical evaluations, CT-P13 active substance was also used; this has a similar formulation (in liquid form) to the finished product. Infliximab was not extracted from the RMP since the formulation does not interfere with the analytical methods used.

Primary and higher order structures

The primary structure of CT-P13 and the RMP was confirmed to be identical by amino acid analysis, sequencing using peptide mapping (in combination with MS/MS), N-terminal sequencing and C-terminal sequencing, except for differences in the levels of C-terminal lysine. In relation to the C-terminal lysine levels, a greater proportion of IgG heavy chain without lysine (K0) in CT-P13 active substance and finished product and lower levels of IgG heavy chain with one lysine (K1), compared with Remicade, were determined under reducing conditions by LC-ESI-MS. Heterogeneity is common for C-terminal lysine in IgG and this is acceptable under the current guidance for similar biological medicinal products; this is unlikely to impact efficacy and safety of the proposed biosimilar product.

The higher order structure of CT-P13 and RMP were shown to be comparable. The positions of disulphide bonds matched (native and reduced peptide mapping) and the free thiol content per mole IgG was similar. Secondary and tertiary structure analysis did not show any significant difference. DSC showed three transition temperatures for the CT-P13 and RMP samples, which were similar for the CT-P13 finished product and Remicade, indicating comparable folding of the proteins. Further structural data was provided using X-ray crystallography of the Fc domains of CT-P13 or Remicade, with identical unit cell dimensions and superimposition of all carbon alpha atoms between the two structures, demonstrating that Fc domains of CT-P13 and Remicade have comparable 3-D structures.

Purity

Differences were observed in purity, with slightly higher levels of aggregates in CT-P13 compared with RMP (SEC-HPLC). This has been discussed by the Applicant, in terms of the relative ages of the CT-P13 and Remicade batches used for the analysis and the monomer content vs. HMW content respectively. No changes were observed over 12 to 33 months storage of either CT-P13 or Remicade. The percentage of monomer exceeded 99% in all cases, including CT-P13 batches stored for 36 months under long-term conditions (5 ± 3°C). Given the low content of HMW species in CT-P13, this is not expected to impact on clinical safety and efficacy. The differences observed are consistent with commonly observed ranges for monoclonal antibodies.

There are differences in the level of intact IgG determined by CE-SDS (non-reduced), with lower levels in CT-P13 finished product than in Remicade batches. The content of the six bands identified by CE-SDS (non-reduced) was determined following extraction and purification with subsequent LC-MS analysis. Both products display the same array of six IgG molecular variants: the main component was two heavy chains and two light chains, H2L2 (the intact IgG monomer), and the main non-assembled CT-P13 form comprised two heavy chains and one light chain, with lower levels of other combinations of heavy and light chains. Therefore, this CT-P13 molecular variant is responsible for much of the difference in intact IgG content between CT-P13 and the RMP. The Applicant demonstrated that the TNFα binding affinity and *in vitro* TNFα neutralising activity were not impacted by increased H2L1 fragment; this justification was considered adequate.

The CT-P13 charged molecular variants have been analysed using IEF, IEC-HPLC, as well as peptide mapping. There are a number of post-translational modifications that have the potential to influence CT-P13 charge heterogeneity, notably C-terminal lysine variability, product deamidation, product oxidation and sialylation. Results from IEF analysis show that the calculated pI values are comparable and fall within similar ranges for CT-P13 active substance, finished product and Remicade samples. Both the CT-P13 and RMP showed six peaks when analysed by IEC-HPLC, but differences were noted in the relative proportions of each peak compared to Remicade. The biological activity of each isolated peak was assessed, demonstrating similar potency by *in vitro* TNFα neutralisation analysis, TNFα binding affinity (by ELISA) and FcRn binding affinity (SPR) for all peaks, although some variability was noted in peak 1 for CT-P13. Comparable results were also observed in C1q binding for CT-P13 compared with Remicade. All isolated IEC-HPLC peaks showed differences in FcγRIIIa binding affinity, with lower values

for the CT-P13 isoforms compared with Remicade. This was confirmed by analysis of CT-P13 and RMP in the biological assays.

The Applicant's conclusion that the difference in IEC-HPLC peak ratio is likely to be the result of C-terminal lysine variability is supported by the CHMP. In order to support the Applicant's position that the difference in IEC-HPLC peak ratio is the result of C-terminal lysine variability, three experimental approaches were undertaken. The data provided justified the Applicant's position and gave assurance that rapid cleavage of the C-terminal lysine occurs in blood following administration of CT-P13. Therefore, the differences in IEC-HPLC peak ratio are unlikely to impact on its bioactivity *in vivo* and thus have no clinically meaningful impact.

Oxidised variants were slightly higher in CT-P13 than in the RMP. An additional study showed that oxidation levels only slightly increase, in either CT-P13 finished product or Remicade under long-term (2-8°C), accelerated (25 ± 2°C/60 ± 5% RH) or stress conditions (40 ± 2°C/75 ± 5% RH), for at least 9 months (CT-P13) or 20 months (Remicade). A significant increase in oxidation was observed in CT-P13 active substance under accelerated conditions for 16 months, but this is expected since the liquid state is more susceptible to oxidation. The forced degradation study demonstrated that a substantial increase in oxidation did not have a substantial effect on potency using the *in vitro* TNFα neutralisation activity and therefore the small increase in oxidation in CT-P13 is unlikely to have an impact. It is noted that the degradation profile of CT-P13 and Remicade is comparable in long-term stability studies. The stability testing has not revealed any differences that could have implications for the safety or efficacy of the CT-P13. According to the results presented by the Applicant, the increased oxidation observed in CT-P13 compared to Remicade is not linked to a decreased bioactivity.

Further information considering the differences in the age of the Remicade and CT-P13 material at time of analyses showed no trends for purity/impurities over storage from 12 to 33 months. In addition, biological activity evaluated by TNFα binding affinity (ELISA), TNFα neutralising activity, apoptosis, CDC, ADCC, FcRn binding affinity and C1q binding affinity, also showed comparable values for the different batches of Remicade and CT-P13 over different storage times. For FcγRIIIa binding affinity by SPR, batches of Remicade showed higher relative affinity compared with CT-P13 finished product but no trends were seen for FcγRIIIa binding affinity in the older batches.

Protein content

Slightly higher protein content was measured in CT-P13 compared to Remicade using the validated UV method. Protein concentration data from further CT-P13 and Remicade batches were submitted to show that this difference is due to batch-to-batch variability of Remicade, and that CT-P13 protein concentration was within the range of the reference product, considering the intrinsic variability of the assay.

Glycosylation

Asn300 was shown to be the only site of N-glycosylation for both CT-P13 and Remicade. No O-linked glycans were detected for CT-P13 or the RMP, as expected for an IgG1 monoclonal antibody. Some differences in the levels of G0, G0F, G2F and the sialic acid containing glycans (higher levels of G1FNeuGc and G2F1NeuGc for CT-P13 finished product compared with RMP) were observed, but in general the glycans were similar in both CT-P13 finished product and the RMP, with no new glycans detected. The main glycans detected in both products are G0F and G1F, typical for IgG. The monosaccharide content of both CT-P13 and RMP were similar for the neutral and amino sugars (molar ratios). The sialic acid analysis demonstrated that both CT-P13 and RMP contain NeuGc at comparable levels. There was a difference in the level of afucosylated glycans, Man5 and G0 for CT-P13 and Man5, G0 and G2 for Remicade, which needs to be considered in relation to the biological activity.

The Applicant has investigated the correlation between glycosylation and Fc function of CT-P13 and Remicade. Reduced glycosylation correlates with lower FcγRIIIa relative binding affinity (using SPR) and lower C1q binding affinity (using ELISA) for both CT-P13 and Remicade. This demonstrated a clear correlation between glycosylation and Fc function and a substantial effect of aglycosylation. In contrast, agalactosylation did not affect FcγRIIIa binding affinity and C1q binding affinity; even with reduction of galactose levels to zero, the relative binding affinities were close to 100%.

Biological activity

No differences between the bioactivity of CT-P13 and Remicade were detected in the *in vitro* TNFα neutralisation assay, the apoptosis assay (using tmTNFα Jurkat cells), the cell-based TNFα binding affinity assay, as well as in the CDC assay. The results were also highly similar for FcγRI, FcγRIIa, FcγRIIb and TNFα binding affinity by SPR, as well as for TNFα and C1q binding affinity by ELISA. The FcRn binding of CT-P13 finished product was also shown to be comparable to Remicade using additional batches of finished product, with overlapping data sets. The potential impact of differences in afucosylation between CT-P13 and Remicade was studied further by using an artificially made highly afucosylated CT-P13 mixed with CT-P13 standard, to give an afucosylation level similar to that of Remicade in these assays. This confirmed that there was no difference in binding to FcγRI, FcγRIIa, FcγRIIb and FcRn (SPR), C1q binding (ELISA) and CDC activity due to differences in core afucosylation levels. No difference in binding activity to TNFα (ELISA or cell-based assay), TNFα neutralisation activity or apoptosis using tmTNFα Jurkat cells was observed using this highly afucosylated CT-P13.

The Applicant has provided more information on the observed binding difference between infliximab in Remsima and Remicade towards FcγRIIIa and discussed the possible reason behind this difference. The Applicant confirmed that V-type FcγRIIIa polymorphic variant was employed in the initial assays submitted in the marketing authorisation application (MAA). The difference has now been confirmed in additional SPR studies using the V-type FcγRIIIa variant. Binding to V-type FcγRIIIa was correlated to the level of fucosylation, demonstrated by significantly reduced binding of CT-P13 compared with the highly afucosylated CT-P13. This difference in binding was also observed with FcγRIIIa F-type hemizygote in the SPR assay. Significantly reduced binding was also observed to FcγRIIIb for CT-P13 compared with Remicade or highly afucosylated CT-P13 which was not unexpected as this receptor has a high sequence homology with FcγRIIIa.

A difference in binding was also shown in *ex vivo* studies on enriched Natural Killer (NK) cells from healthy donor PBMC: for the high affinity binding FcγRIIIa receptor 158V/V genotype, a decrease in binding of CT-P13 compared to Remicade was detected. A similar decrease in binding was also seen for the 158V/F genotype while no difference between CT-P13 and Remicade was observed for the 158F/F genotype. These binding studies were extended to include NK cells derived from Crohn's disease patients of all genotypes, with reduced binding for CT-P13 (in V/V genotype and V/F genotype) compared with Remicade, but no difference in overall mean binding using NK cells from patients of F/F genotype. Binding of CT-P13 and Remicade to NK cells was also performed in the presence of diluted Crohn's disease patient serum, to mimic the *in vivo* environment. This showed an overall reduction in total binding, but the level of residual binding was comparable, showing an abrogation of the difference in binding previously seen with CT-P13 and Remicade (in the absence of serum) for V/V and V/F genotypes. It is suggested that this reduction in overall binding and abrogation of any observed differences is due to the presence of immune complexes, soluble serum factors and/or monomeric IgG in the serum. Therefore the relevance of binding differences to FcγRIIIa on NK cells, observed under more stringent *in vitro* conditions, may not be extrapolated into a clinical effect in patients.

Binding of CT-P13, Remicade or the highly afucosylated CT-P13 to neutrophils from healthy donors or Crohn's disease patients was studied *in vitro* to examine binding to FcγRIIIb receptors in a more native conformation on the surface of relevant cells *in vitro.* There were no differences in binding to neutrophils,

which have high levels of FcγRIIIb as well as FcγRI and FcγRIIa on the cell surface. Therefore, differences in binding of CT-P13 and Remicade to FcγRIIIb in the SPR assay did not translate to a difference in binding to healthy donor or Crohn's disease patient neutrophils.

The Applicant has also provided ADCC activity data from additional CT-P13 and Remicade batches using healthy donor PBMC (V/F genotype). Dose-response results were provided and the results did not indicate any differences in the ADCC responses between CT-P13 and Remicade. Accuracy, intermediate precision, repeatability and specificity were determined for the ADCC assay, with acceptable results. Sensitivity of the ADCC assay was evaluated by comparing deglycosylated and afucosylated CT-P13 to untreated CT-P13 samples, using Jurkat cells expressing tmTNFα as target cells and PBMC as effector cells. These studies demonstrated the sensitivity of the ADCC assay, but only at higher levels of afucosylation. The ADCC assay was not able to discriminate between samples where the afucosylation level was below 12%. This raised concern initially, as it was questionable whether the ADCC assay using PBMC effector cells was sensitive enough to detect potential differences between the biosimilar and the originator.

The sensitivity of the ADCC assay was improved using NK cells as effector cells in this assay, with confirmation that ADCC is dependent on glycosylation and influenced by core fucose levels. Significant differences were noted in the cytotoxic response in this assay for CT-P13 and Remicade, using NK cells from Crohn's disease patients of V/V and V/F genotypes but not the F/F genotype. This was consistent with the binding data shown with enriched NK cells and also the levels of afucosylation in CT-P13 and Remicade. The reason for differences in ADCC using NK cells but not PBMC is likely to be attributed to the mixed cell population present in PBMC, with multiple Fc receptors available for binding to CT-P13 and Remicade. This was further evaluated by using whole blood as effector cells in the ADCC assay, with comparable ADCC responses noted with CT-P13 and Remicade. Therefore, under conditions more representative of the *in vivo* situation (PBMC or whole blood), the difference in fucosylation for CT-P13 and Remicade does not have any impact on ADCC.

Further investigation was undertaken to examine any likely impact in patients, since differences observed in binding to FcγRIIIa were not confirmed by differences in ADCC using PBMC from healthy donors as effector cells and tmTNFα Jurkat cells as target cells in previous studies. No differences were observed in ADCC for CT-P13 or Remicade using PBMC from Crohn's disease patients of V/F or F/F genotype, although a lower dose-response curve was observed with PBMC from Crohn's disease patients compared with healthy donor PBMC (V/F genotype). This lower response may be attributed to the lower number of NK cells and CD16 expression levels measured in Crohn's disease patient PBMC compared with healthy donor PBMC. A previous study had shown that cytotoxicity in rheumatoid arthritis patient PBMC was essentially abrogated compared with healthy donor and Crohn's disease patient PBMC, although the genotype of this rheumatoid arthritis patient was not specified.

In addition, lipopolysaccharide (LPS)-stimulated monocytes were used as target cells in the ADCC assay, to mimic the *in vivo* inflammatory situation. No ADCC response was detected using LPS-stimulated monocytes from healthy donor (V/F) or Crohn's disease patient (V/F) as target cells. The fact that ADCC can only be detected when using tmTNFα Jurkat cells as target cells which have much higher levels of tmTNFα, suggests that ADCC may be limited or absent under physiological conditions *in vivo*.

Additional Fc-mediated biological activity was explored to determine if the difference in fucosylation between CT-P13 and Remicade is likely to have an impact *in vivo*. Induction of regulatory macrophages and inhibition of T-cell proliferation using a two-way allogeneic mixed lymphocyte reaction demonstrated no difference between CT-P13 and Remicade, for all genotypes (V/V, V/F and F/F) from either healthy donors or Crohn's disease patients. The biological activity of the CT-P13, Remicade or the highly afucosylated CT-P13 induced regulatory macrophages was compared in an *in vitro* wound healing model using human colon epithelial cells. No differences in the closure of a scratch in the cell monolayer

could be detected, confirming that the different level of fucosylation does not impact the biological activity when conditions are used which mimic the *in vivo* situation.

Dose-dependent suppression of pro-inflammatory cytokines and inhibition of apoptosis was also demonstrated in a model of inflammation using a human intestinal epithelial cell line, to support the extrapolation to inflammatory bowel disease.

In conclusion, a comprehensive battery of *in vitro* assays has been applied to characterise biological activity. The assays used are specific to Remsima (CT-P13) and have been suitably justified during the assessment of this MAA. In some cases, differences were identified; Remsima exhibits a lower level of afucosylated glycans than Remicade, hence a lower binding affinity to FcγRIIIa and a lower activity in the most sensitive ADCC assay using NK cells as effector cells and tmTNFα Jurkat target cells. However, no difference could be detected in several experiments that are more representative of pathophysiological conditions, and therefore more relevant clinically (e.g. in blood, in a mixed lymphocyte reaction from FcγRIIIa genotype matched PBMCs with induction of a subset of regulatory macrophages, in a wound healing model using induced cells that include these macrophages on a culture of human colorectal epithelium cells).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Remsima is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Biosimilarity with the reference medicinal product Remicade has been sufficiently demonstrated. From a quality point of view, the observed differences and levels of these differences have been well documented and are acceptable.

The overall Quality of Remsima is considered acceptable.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical comparability program versus Remicade included pharmacodynamic (PD), pharmacokinetics (PK) and toxicological studies. The non-clinical data consisted in several *in vitro* primary PD studies (including a human tissue cross reactivity study comparing CT-P13 and Remicade), 2 pivotal toxicology studies (one with toxicokinetics [TK] and immunogenicity testing) and 1 PK study in order to compare the bioactivity profiles of CT-P13 with Remicade. In addition, a dose-range-finding study investigating the toxicity, TK and immunogenicity of Remicade has been conducted.

The nonclinical development program with CT-P13 was performed in agreement with the CHMP scientific advices (EMEA/CHMP/SAWP/572897/2009 Procedure No.: EMEA/H/SA/1385/1/2009/II and the Follow up EMEA/CHMP/SAWP/788787/2009 Procedure No.: EMEA/H/SA/1385/1/FU/1/2009/II). The nonclinical development program was performed according to the EMA guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) and on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005) and with ICH guideline S6 (RI) –preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5 (EMA/CHMP/ICH/731268/1998).
The *in vivo* comparative 2 week toxicity studies in rats and immunohistochemistry study of cross-reactivity in human tissues were performed in compliance with GLP requirements.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The biological activity of infliximab can be categorised into two parts. The primary mechanism of action involves the TNFα neutralisation by binding to TNFα and inhibition of cell signalling for proliferation. Assays for this include *in vitro* TNFα neutralisation activity, apoptosis, TNFα binding affinity (Surface Plasmon Resonance (SPR)), TNFα binding affinity (ELISA) for potency measurements, and cell-based TNFα binding affinity. The secondary mechanism of action involves the activation of the immune responses which includes ADCC, CDC, FcγR family binding affinity (SPR), FcRn binding affinity (SPR) and C1q binding affinity (ELISA).

Primary PD consisted of 33 *in vitro* studies assessing the binding affinity of CT-P13 and Remicade to soluble (from different species) and transmembrane form of human TNFα, TNFβ, FcγRI, FcγRIIa, FcγRIIIa, FcRn and C1q; the TNFα neutralisation activity; the CDC, ADCC, apoptotic effects; and the cross-reactivity with various human tissues.

Remicade was included as reference product in all of these studies.

The type, test method used and key findings of these studies can be found in the quality section 2 of this report

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed. No requirements for secondary pharmacodynamics studies have been detailed in relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). Off-target toxicological investigations have been performed in repeat-dose toxicity studies using the rat, with comparable off-target findings observed in this species.

Safety pharmacology programme

No safety pharmacology studies have been performed in line with CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), which states that safety pharmacology studies are not required for non-clinical testing of biosimilar mAbs.

Pharmacodynamic drug interactions

No comparative studies assessing PD drug interactions have been performed with CT-P13. No requirements for PD drug interactions studies have been detailed in relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.3. Pharmacokinetics

The PK data consisted in a single study in rats (Study N09067), supported by validation of methods to detect and quantify CT-P13, Remicade and antibody formation performed for GLP studies.

Method of analysis

Methods for detection of infliximab rat serum levels from exposure to CT-P13 and Remicade by ELISA methodology, and for the measurement of anti-CT-P13 antibody and anti-Remicade antibody concentration in rat serum by semi-quantitative ELISA assays were developed and validated for GLP studies..

Absorption

Study N09067: single intravenous dose pharmacokinetics comparison study in rats

In this study to compare the PK of CT-P13 and Remicade, a total of 20 male Sprague-Dawley rats received a single IV administration of CT-P13 or Remicade at a dose level of 10 or 50 mg/kg (5 rats/dose group). Serum samples were collected over 336 h after administration of CT-P13 or Remicade. CT-P13 or Remicade serum levels were quantified by an ELISA assay. The determination of comparability was based on comparison of the AUC_t.

No deaths were observed during the study. There were no treatment-related changes in the clinical observations. After a single IV administration of CT-P13, the serum concentrations of infliximab slowly declined in bi-exponential manner. The area under the serum concentration-time curve from the start of dosing to the time of last sampling (AUC_{0-t}), the back extrapolated concentration at time zero (C_0) and the maximum observed peak serum concentration (C_{max}) increased in a dose-proportional manner with increasing dose between 10 to 50 mg/kg. The serum concentration-time profiles for CT-P13 and Remicade are shown below.

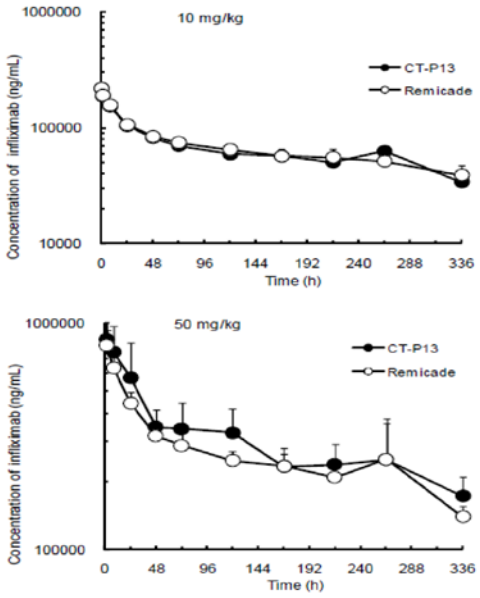


Figure 3 Mean serum concentrations of infliximab after intravenous administration of CT-P13 and Remicade in rats

After a single dose IV administration of CT-P13 or Remicade at 10 and 50 mg/kg, the serum concentration-time profiles of CT-P13 and Remicade were similar. The geometric mean AUC_{0-t} ratio of CT-P13 and Remicade was 96.66% (90% CI 79.69 to 117.23) at 10 mg/kg. At 50 mg/kg, the geometric

mean AUC_{0-t} ratio of CT-P13 and Remicade® was 112.70% (90% CI 87.30 to 145.49). The PK parameters obtained from this study are summarised in the tables below

Table 9 Comparability of CT-P13 over Remicade after single intravenous administration in rats

Dose (mg/kg)	AUC_t (ng h/mL)	Reference (Remicade®)	Test (CT-P13)	90% CI*
10	$LnAUC_t$ **	16.9208 ± 0.0734	16.8868 ± 0.0734	79.69 - 117.23
	geometric mean	22316480.0	21570467.7	(96.66)***
50	$LnAUC_t$ **	18.3098 ± 0.0971	18.4294 ± 0.0971	87.30 - 145.49
	geometric mean	89504276.5	100872474.1	(112.70)***

* 90% confidence interval based on logarithmic transformed AUC_t
** logarithmic transformed AUC_t
*** geometric mean ratio of CT-P13 over Remicade®

Table 10 PK comparability of infliximab after single intravenous administration of CT-P13 and Remicade in rats

Gender (M/F) / Number of animals	M/5	M/5	M/5	M/5
Method of Administration	Intravenous	Intravenous	Intravenous	Intravenous
Dose (mg/kg)	10 mg/kg (CT-P13)	50 mg/kg (CT-P13)	10 mg/kg (Remicade®)	50 mg/kg (Remicade®)
Mean C_{max} (ng/mL)	216894.9	1191346.6	219959.6	1050988.4
Mean t_{max} (h)	0.25	0.25	0.25	0.25
Geometric mean AUC_t (ng·h/mL)	21570467.7	100872474.1	22316480.0	89504276.5
Arithmetic mean AUC_t (ng·h/mL)	21953242.0	103575665.4	22404400.9	90362460.3
MRT_t (h)	136	134	136	137

Distribution

No distribution studies have been performed in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Metabolism and excretion

No metabolism studies have been performed with CT-P13 in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). Infliximab is composed of amino acids and carbohydrates like endogenous immunoglobulins, such that its metabolism and excretion will be the same as for normal immunoglobulin clearance pathways.

PK drug interaction

No studies assessing pharmacokinetic drug interactions have been performed with CT-P13 in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity study was performed in line with the CHMP guideline on studies required for

similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) and the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Repeat dose toxicity

Two 2-weeks repeat dose toxicity studies in rats were performed to compare off-target toxicity profiles of CT-P13 and Remicade. Initially, an exploratory dose-finding study was also performed with Remicade in rats to confirm dose selection of the comparative studies.

Table 11 Summary of repeat-dose toxicity studies performed with CT-P13 and Remicade

Study ID	Species/Sex/ Number/Group	Dose (mg/kg) / Route	Duration	NOAEL (mg/kg/day)	Major findings
8214167*	Rat / M&F / 5	0, 10, 40 IV Remicade	2 doses 1 week apart	40 mg/kg	No major toxicity
8214158	Rat / M&F / 10	0, 10, 40 IV CT-P13 & Remicade	2 doses 1 week apart	40 mg/kg	No major toxicity; the two drugs are comparable
G09197	Rat / M&F / 10	0, 10, 50 IV CT-P13 & Remicade	2 doses 1 week apart	50 mg/kg	No major toxicity; the two drugs are comparable

* No claim of GLP compliance is made for this study. IV= intravenous, M=male, F=female, NOAEL=no observed adverse effect level

- **Study 8214167: 2-Week IV injection dose finding study with Remicade in rats**

In an initial study, non-GLP-compliant, toxicity and toxicokinetics (TK) of Remicade were evaluated in 5 male and 5 female rats, aged 11 weeks old, who were dosed with a bolus IV injection of Remicade twice, on Day 1 and day 8 at doses of 0, 10 or 40 mg/kg. Controls were given 0.9% sodium chloride. Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption, opthalmoscopy and pathology. All animals were sacrificed on day 15 and subject to necropsy. Further male and female rats were similarly dosed for TK evaluation.

Dosage analyses indicated that test article concentrations were within 92.3-94.6% of nominal values. There were no unscheduled deaths in the toxicity study and Remicade was well-tolerated with only minor clinical abnormalities noted after dosing (e.g. hypoactivity and/or eye squinting). There was no toxicity noted on body weight, body weight changes or in food consumption. Slightly higher reticulocyte and platelet counts were noted in males at 40 mg/kg but were considered incidental. There were no findings indicating toxicity at necropsy and all abnormalities were judged incidental and not related to Remicade. The NOAEL was set at 40mg/kg. At this dose, C_{max} values following dosing on day 8 were 1.2 mg/ml in males and 8.7 mg/ml in females and AUC values were 88.4 mgh/ml in males and 73.5 mgh/ml in females. Measures of exposure were approximately in proportion between the two doses 10 and 40 mg/kg and differences between males and females were less than 2-fold. Assay of serum samples for anti-infliximab antibodies was done. Of 84 test samples tested, there was one with a positive result, but this was from a pre-dose sample and a confirmatory test result was negative.

- **Study 8214158: 2-Week repeat-dose IV toxicity and TK study with CT-P13 and Remicade in rats**

In this GLP-compliant study, 10 male and 10 female rats, aged 10-11 weeks old, were dosed by IV bolus injection with CT-P13 or Remicade on two occasions, one week apart at doses of doses 0, 10 or 40 mg/kg. Controls were given 0.9% sodium chloride. Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption, ophthalmoscopy and pathology. Animals were sacrificed

on day 15 and subject to necropsy. Further male and female rats were similarly dosed for TK evaluation. Also, blood was collected by cardiac puncture on day 15 after carbon dioxide anaesthesia.

Dosage analyses indicated that test article concentrations were within 98.8-100 and 93.2-94.4% of nominal values for CT-P13 and for Remicade, respectively. There were no unscheduled deaths in the main toxicity study. In TK groups, one female at 10 mg/kg CT-P13 was found dead on day 4 after the 72 hour blood sample. This was not judged test-article-related. There were no clinical observations indicating toxicity and no toxic effects were seen on body weight, body weight change, except for a marginal decrease in body weight gain in females given 40 mg/kg CT-P13 compared to controls, nor in food intake, or at ophthalmoscopy. Whereas there were some changes in clinical pathology parameters, these were judged to be minor and not of toxicological importance. For instance, there was an increase in absolute reticulocyte counts at 40 mg/kg of each test article in males and also of platelets at this dose in females; haemoglobin was statistically different from controls but was elevated at 10 mg/kg CT-P13 (from 15.9 to 16.4 g/dl) and was reduced at 40 mg/kg (from 15.9 to 15.5 g/dl). Such changes were not considered to be toxicologically significant and these had no correlated change in tissues on microscopic examination. At necropsy, there was an increase in the relative (to brain) weight of the uterus in females given 40 mg/kg CT-P13 and in females given 10 mg/kg Remicade but this was attributed to normal variation. There were occasional findings on microscopic examination, but these were all attributed to normal biological variation. Minimal Kupffer cell hyperplasia was present in 2/10 and in 7/10 males given 10 or 40 mg/kg CT-P13 and was present in 2/10 and in 6/10 females at these doses; however, this was also present in 4 and 3/10 males and females and 7 and 7/10 males and females at 10 and 40 mg/kg Remicade. This was likely test-article-related but was not adverse due to minimal severity. There was also individual lymphocyte necrosis in the thymus of rats given either dose of either test article. This reflected normal biological variation but also a test-article-related effect cannot be ruled out. Injection sites were examined and a minimal degree of inflammation was commonly reported but this was no more common in those given the active agents than in controls. In conclusion, it was determined that the no observed adverse effect level (NOAEL) was 40 mg/kg for both CT-P13 and Remicade and that the effects were similar for both test articles.

- **Study G09197: 2-Week IV dose toxicity comparison study in rats (CT-P13 and Remicade)**

In a second GLP-compliant study, 10 male and 10 female rats, aged 6-7 weeks old, were dosed intravenously with CT-P13 or with Remicade on two occasions, one week apart at doses of doses 0, 10 or 50 mg/kg. Controls were given 0.9% sodium chloride. Assessment of toxicity was based on the same parameters as previous study and animals were sacrificed on day 15 and subject to necropsy. Further male and female rats were similarly dosed for TK evaluation. Also, blood was collected by cardiac puncture on day 15 after carbon dioxide anaesthesia.

There were no unscheduled deaths. Transient subdued behaviour was noted at 50 mg/kg of each teat article. There were no changes in body weight or in the change in body weight over the monitoring period, although there was a reduction in food intake at 50 mg/kg of each of CT-P13 and Remicade. There were no abnormalities noted in ophthalmological examination, or on urinalysis. In haematology, there were increases in reticulocytes (1.27 – 1.46 fold) and in platelets (1.22-1.24) at 50 mg/kg of each test article. Decreases in creatinine kinase were found (to 0.64-0.68 fold) at 50 mg/kg of each test article. At post mortem examination, there were increases in the relative liver weight (1.09-1.11 fold) of females at 50 mg/kg of each test article and also an increase in absolute liver weight (1.12-1.13 fold) of females given either 10 or 50 mg/kg Remicade. There were no abnormalities on histopathological examination attributed to treatment with either test article. No differences in toxicity between CT-P13 and Remicade were detected. All treatment-related changes described above including clinical signs, food consumption, haematology, serum biochemistry, and organ weights showed similar patterns in the animals given

CT-P13 and Remicade at both, 10 and 50 mg/kg/dose. It was concluded that the NOAELs for CT-P13 and Remicade were both 50 mg/kg/dose, with comparable findings observed for both test articles.

Genotoxicity

No genotoxicity studies have been performed. The CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) states that other routine toxicological studies such as mutagenicity (genotoxicity) and carcinogenicity are not required for similar biological medicinal products, unless indicated by results of repeat-dose studies. The CHMP guidance on similar biological medicinal products containing monoclonal antibodies states that mutagenicity (genotoxicity) studies are not routinely required (EMA/CHMP/BMWP/403543/2010). Large proteins, such as monoclonal antibodies, are not expected to pass through cell membranes and interact directly with DNA or other chromosomal material. In addition, as data obtained from the repeat-dose toxicity studies have not indicated any cause for concern, it is considered that genotoxicity and/or carcinogenicity studies are not necessary for this product.

Carcinogenicity

Carcinogenicity studies have not been performed in line with the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), which states that carcinogenicity studies are not routinely required and should only be performed for cause. The CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) also states that routine toxicological studies such as carcinogenicity are not required for similar biological medicinal products. There is no cause for concern from previous animal studies conducted. The SmPC for CT-P13 addresses malignancies/cancer development in man in line with the SmPC of Remicade.

Reproduction Toxicity

Reproductive and developmental toxicity studies have not been performed. The CHMP Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/ 403543/2010) states that reproduction toxicity studies are not routine requirements for non-clinical testing of similar biological medicinal products containing monoclonal antibodies as active substances. Likewise, the CHMP guidance on biosimilar medicinal products (EMEA/CHMP/BMWP/42832/2005) states that routine toxicological studies, such as reproduction and developmental toxicology are not required.

Toxicokinetic data

TK analysis from study 8214158 showed exposure to CT-P13 and Remicade increased with the increase in dose level from 10 to 40 mg/kg/dose. Increases in C_0, C_{max}, and AUC_{0-168} after dosing with CT-P13 or Remicade were generally dose proportional and sex differences were less than 2-fold. Potential accumulation of CT-P13 and Remicade was observed after the second dose. CT-P13 to Remicade ratios for C_{max} and AUC_{0-168} values are presented below; in all cases, values for CT-P13 are lower than those for Remicade.

Table 12 Summary of CT-P13 to Remicade ratios for C_{max} and AUC_{0-168} values

Day	Dose Level (mg/kg/dose)	Sex	CT-P13: Remicade Ratio	
			C_{max}	AUC_{0-168}
1	10	Male	0.794	0.822
		Female	0.907	0.901
	40	Male	0.933	0.863
		Female	0.811	0.696
8	10	Male	0.759	0.782

		Female	0.916	0.846
	40	Male	0.840	0.791
		Female	0.646	0.680

When compared to Remicade, CT-P13 C_{max} and AUC_{0-168} values were generally 8.40% to 24.1% and 6.70% to 35.4% lower at the 10 and 40 mg/kg dose levels, respectively. However, these lower results appear to be caused by the mean concentration-time data from a composite profile being used in the TK parameter calculation in this study (3 rats/timepoint rather than sampling the same individuals over the full monitoring period); these data were limited due to a sparse nature of TK sampling.

Nine animals/sex assigned to each dose group of CT-P13 or Remicade for the TK study were divided into 3 sub-groups for blood sampling at each time interval. Blood samples were taken from each sub-group, 3 animals/sex, and the mean serum concentration at each sampling time point was used to calculate the TK parameter. Due to this kind of TK sampling approach, only one value of TK parameters for each dose group of CT-P13 or Remicade could be calculated. As a result, the TK study result was thought to have excessive variation. This was confirmed when comparing TK parameters obtained from the animals treated with the same batch and dose levels of Remicade in 2 TK studies (Study 8214167 and 8214158) because the ratio of C_{max} and AUC_{0-168} for the same Remicade dose varies from 103.6% to 149.6% and 104.8% to 132.1% respectively over the sex, dose levels and dosing phases from the studies.

Local Tolerance

No separate local tolerance studies have been performed. Histopathological assessments of local (injection site) tolerance were carried-out in the repeat-dose toxicity studies. In Study 8214158, there were no toxicologically significant differences in injection site findings between control animals and the animals at the high doses of CT-P13 and Remicade (injection sites of the low doses were not histopathologically examined). In Study G09197, there were no injection site findings in control animals and in the animals at high doses of CT-P13 and Remicade (injection sites of the low doses were not histopathologically examined). This is in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) which states that studies on local tolerance are usually not required and that if other *in vivo* studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies.

Other toxicity studies

Studies into dependence, metabolites, and impurities have not been performed. Immunogenicity of CT-P13 in comparison with Remicade was assessed as part of the 2-week repeat-dose toxicity study 8214158 in rats. The formation of the antibodies against CT-P13 and Remicade was assessed in 167 samples in total. The results showed that no anti-infliximab antibodies were detected in animals that received either CT-P13 or Remicade. Based on these data, no further evaluation for neutralising antibodies was conducted. No other toxicity studies have been conducted.

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment was performed in line with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) which states that proteins are exempted from the need for an assessment of impact on the environment because they are unlikely to result in significant risk to the environment. CT-P 13 is a monoclonal antibody and is a protein; therefore an environmental risk assessment is not required for this medicinal product

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics study package consisted of *in vitro* studies assessing the binding affinity of CT-P13 (and Remicade) to soluble monomeric and trimeric form of TNFα and transmembrane form of TNFα, TNF_{β}, FcγRI, FcγRIIa, FcγRIIIa, FcRn and C1q; the TNFα neutralisation activity; the complement – dependent cytotoxic (CDC), antibody-mediated cytotoxic (ADCC) and apoptotic effects; and the cross-reactivity with various human tissues. Thus, in accordance with CHMP Guideline EMA/CHMP/BMWP/403543/2010, this testing addressed binding to the target antigen, binding to Fcγ receptors, FcRn and complement, Fab-associated properties of functional neutralisation and Fc-associated properties (ADCC, CDC and complement activation).

All comparative *in vitro* primary pharmacodynamics studies results between CT-P13 and Remicade are discussed in the quality section 2 of this report. In summary, In terms of the binding affinity to TNFα, equilibrium dissociation constant K_D assessed by ELISA and the kinetics assessed by SPR for soluble monomeric and trimeric TNFα, CT-P13 and Remicade were comparable showing nearly identical K_D values. Other studies assessing the binding affinity to the monomeric and trimeric forms of TNFα and transmembrane TNFα, show comparable results for CT-P13 drug product and Remicade. Comparable binding affinities to FcγRI, FcγRIIa and FcRn were shown. A difference in the binding affinity to the FcγRIIIa was seen with the CT-P13 as compared to the RemicadeThe identified difference in FcγRIIIa binding was further investigated during the procedure and is discussed in the quality section 2 of this report under biological activity and in the clinical section 3 under extrapolation of efficacy and safety. The Applicant did not present any data on secondary pharmacology, safety pharmacology or pharmacodynamic drug-drug interactions. This is consistent with CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Pharmacokinetics

Comparative PK between CT-P13 and Remicade was evaluated in the single IV dose study N09067 in rats at two dose levels, 10 and 50 mg/kg. The methods to detect and quantify CT-P13, Remicade were appropriately validated. Method validations were performed in compliance with the GLP. Comparability was evaluated based on the ratio of the geometric means of the area under the curve. Following a single IV injection of CT-P13 or Remicade, the serum concentration slowly declined generally in a bi-exponential manner and the AUC_t and C_{max} increased in a dose-proportional manner with increasing dose from 10 to 50 mg/kg. The geometric mean AUC_{0-t} ratio of CT-P13 compared to Remicade at 10 and 50 mg/kg were 96.66 (90% CI 79.69 to 117.23) and 112.70% (90% CI 87.30 to 145.49) respectively. The observed variability is reasonably linked to the small sample size used (a human bioequivalence study would not use as small a number as 5 per group). Although hampered by methodological limitations, the other PK parameters [C_{max}, T_{max}, MRT_t] also showed similar results for the two formulations. Overall, a difference in the PK of CT-P13 and Remicade after IV administration at doses of 10 and 50 mg/kg is not suggested and it can be concluded the PK of CT-P13 after IV administration at doses of 10 and 50 mg/kg are similar to those of Remicade.

The absence of studies into distribution, metabolism, excretion and PK drug-drug interactions is consistent with CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Toxicology

Three repeat-dose toxicity studies in rats were performed to evaluate the safety of CT-P13. Due to the lack of cross-reactivity of infliximab with any species other than chimpanzee or human, these studies

were performed to compare general off-target product toxicity (including immunogenicity) of CT-P13 with Remicade. Studies in species other than chimpanzee are not capable of identifying target-related toxicity.

Study 8214167 was a pilot exploratory dose-finding study performed with Remicade in rats which confirmed that a dose level up to 40 mg/kg given IV, on two occasions, one week apart did not reveal any significant adverse effects and therefore would be suitable for further testing. The study was not comparative in nature and did not involve CT-P13. Two GLP-compliant repeat dose toxicity studies 8214158 and G09197 were then performed in rats dosed intravenously with either CT-P13 or Remicade at 0, 10 or 40 mg/kg (study 8214158) and at 0, 10 or 50 mg/kg (study G09197). In both studies, two doses were given one week apart. No significant test-article related findings were noted in any of the studies. In the first study, minimally higher absolute reticulocyte count in males and mildly higher platelet count in males and females at 40 mg/kg/dose CT-P13 or Remicade, as well as minimal Kupffer cell hyperplasia in livers at 10 and 40 mg/kg/dose CT-P13 or Remicade were observed. However, the changes were of similar magnitude for both test articles. The NOAELs for CT-P13 and Remicade were both 40 mg/kg/dose infliximab. In the second study, subdued behaviour, decreases in food consumption, changes in creatine kinase, and albumin/globulin ratio, increases in platelets and reticulocytes (%), total protein and female liver weights were observed. The findings were comparable for CT-P13 and Remicade. The NOAELs for both products were the same 50 mg/kg/dose. In terms of off-target toxicity CT-P13 can be considered biosimilar to Remicade. However, due to the lack of primary pharmacodynamic activity in rats, toxicity testing conducted was not relevant to judging comparability between CT-P13 and Remicade or to predicting safety in human.

Immunogenicity analysis from study 8214158 showed that none of the serum samples from treated animals were positive with antibodies to CT-P13 or Remicade.TK results from the study indicated that animals were almost continuously exposed to CT-P13 or Remicade throughout the study. Exposure to CT-P13 and Remicade increased with the increase in dose level from 10 to 40 mg/kg/dose. Increases in C_0, C_{max}, and AUC_{0-168} after dosing with CT-P13 or Remicade were generally dose proportional and sex differences were less than 2-fold.

The absence of testing for single dose toxicity, genotoxicity, carcinogenicity and reproduction toxicity is acceptable and consistent with CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). Local tolerance at the injection sites was evaluated in the repeat-dose toxicity studies following 2 weekly IV injections of CT-P13 or Remicade. No irritation or other injection site reactions were noted with either of the products. However, instead of the final formulation intended for clinical use a saline vehicle for CT-P13 and Remicade was used. Hence, no conclusions on clinical tolerability of the final drug product formulation can be made based on these animal data. However, CT-P13 seemed well tolerated in clinical use, and there is no need for additional local tolerance study.

An environmental risk assessment is not required according to the CHMP guidance on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 1) as CT-P13 is a protein and proteins are unlikely to result in significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

In accordance with the Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) and biotechnology-derived proteins as active substance; non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005) and with ICH guideline S6 (RI)– preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5 (EMA/CHMP/ICH/731268/1998), the Applicant has performed state-of-the-art comparative characterisation studies between CT-P13 and Remicade.

The pharmacological study package is considered adequate and thorough. The comparability of the CT-P13 drug to the reference medicinal product was shown in the majority of parameters assessed. Some variability was seen in the results which is acceptable. All comparative *in vitro* primary pharmacodynamics studies results were presented and discussed in the quality section of this report. The difference observed in FcγRIIIa binding was further discussed and analysed in the quality and clinical section of this report. Overall it was concluded that this observation does not impact the biological activity (when conditions more representative of the *in vivo* situation are used) and, with a high level of probability, has no clinically relevant impact of the efficacy and safety of CT-P13.

Study N09067 was the only comparative single dose PK study performed in rats with CT-P13 and Remicade, each at either 10 or 50 mg/kg given IV. The geometric mean AUC_{0-t} ratio of CT-P13 compared to Remicade at 10 and 50 mg/kg were 96.66 (90% CI 79.69 to 117.23) and 112.70% (90% CI 87.30 to 145.49) respectively. The degree of variability showed may be attributed to the small sample used in each group. Overall, the PK of CT-P13 and Remicade after IV administration in rats at doses of 10 and 50 mg/kg are considered similar. Repeat dose toxicity evaluation in the non-responsive species rat revealed no significant test-article related off-target toxicity. The minimal treatment related findings were of similar magnitude and frequency with both CT-P13 and Remicade. In terms of off-target toxicity CT-P13 can be considered biosimilar to Remicade. However, as infliximab is not active in rats, these studies are not relevant for predicting human safety and are of little relevance for determining biosimilarity. Overall, there appear to have no difference in PK in rats between CT-P13 and Remicade as well as in relation to general toxicity.

The absence of other types of testing (secondary and safety pharmacology, distribution, metabolism, excretion, genotoxicity, carcinogenicity and to reproductive function) is agreed as is the absence of an assessment of risk to the environment. The lack of these data is acceptable and consistent with CHMP guidelines. Sections 4.6 and 5.3 of the SmPC for CT-P13 reflect the same information as for Remicade.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme to show biosimilarity between CT-P13 and Remicade consists in two pivotal trials:

- Study CT-P13 1.1: a comparative pharmacokinetic (PK) study in patients with AS
- Study CT-P13 3.1: a study comparing the efficacy and safety of CT-P13 and Remicade in patients with active RA.

These 2 studies were planned with a 1-year treatment duration. In both case the primary endpoints were assessed at 30 weeks (when the 6th infusion was administered). Results at Week 30 served as basis to support this application. During the assessment the Applicant submitted further efficacy and safety data up to 54 weeks.

A third study (CT-P13 1.2) in RA patients was a small pilot study performed primarily to facilitate the conduct of the pivotal trial CT-P13 3.1. It was on-going (up to 2 years of treatment) at the time of this procedure.

The same study product was used in the three clinical studies. Supplies of the reference product Remicade were sourced from 15 batches in the EU with manufacture dates ranging from September 2009 to September 2011.

GCP

The clinical trials were conducted in accordance with GCP as claimed by the Applicant. The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. In the study CT-P13 1.1 and 3.1 one centre was closed due to a suspected misconduct. The data from this centre were excluded from the statistical analyses.

A request for a routine GCP inspection (INS/GCP/2012/11) was adopted by the CHMP for the following clinical study: CT–P13 3.1: a randomised, double – blind, parallel – group, phase III study to demonstrate equivalence in efficacy and safety of CT–P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis. The inspections took place at three investigators' sites. Based on the GCP inspection findings, the CHMP concluded that the study had been conducted in compliance with GCP at these sites. Overall, the CHMP considered that the patients in this study had received acceptable information about the conduct of the study and that the subjects were well taken care of by the professional study team. No critical findings were identified during the inspections and it is the opinion of the CHMP that the data documented and reported in the study are credible and can be used for evaluation and assessment of the application.

Table 13 Tabular overview of clinical studies

Protocol	Design	Objectives	Treatment	Study population
CT-P13 1.2 (pilot study)	Prospective Phase 1, randomised double-blind, parallel-group, multiple single-dose intravenous (i.v.) infusion, multicentre	Primary: To determine C_{max}, PK profiles of CT-P13 and Remicade at Weeks 0, 2 and 6 Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to Remicade up to Week 102.	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 20 Randomised: 19 CT-P13: 9 Remicade: 10
CT-P13 1.1 PK equivalence (Study name: PLANET AS)	Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate comparable PK at steady state in terms AUC_T, $C_{max,ss}$ between CT-P13 and Remicade determined between Weeks 22 and 30. Secondary: long-term efficacy, PK and overall safety up to Week 54	CT-P13 or Remicade	AS patients with active disease Planned: 246 (ratio: 1:1) Randomised: 250 CT-P13: 125 Remicade: 125
CT-P13 3.1 Therapeutic equivalence (Study name: PLANET RA)	Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate that CT-P13 is equivalent to Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30. Secondary: long-term efficacy, PK, PD, and overall safety up to Week 54	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 584 (ratio: 1:1) Randomised: 606 CT-P13: 302 Remicade: 304

ACR20=20% improvement according to the ACR criteria; AS=Ankylosing spondylitis; AUC_T=Area under the concentration-time curve over the dosing interval; Cmax=maximum serum concentration; i.v.=intravenous; MTX=methotrexate; PK=Pharmacokinetics; PD=Pharmacodynamics; RA=Rheumatoid arthritis

2.4.2. Pharmacokinetics

Introduction

The PK profile of CT-P13 was investigated in the 3 above-mentioned clinical studies and compared with that of Remicade. Immunogenicity was also monitored in all 3 clinical studies. The studies were randomised, double-blind, parallel-group and comparator-controlled studies. In accordance with the

guideline on similar biological medicinal products containing monoclonal antibodies, the primary objective of PK studies was to show comparability in PK of CT-P13 with Remicade in a sensitive and homogeneous population.

Analytical methods

The serum concentrations of infliximab were measured using a validated sandwich immunoassay. Anti-drug antibodies (ADA) were determined with an electrochemiluminescent (ECL) immunoassay method. The same assay using Remicade as the immunocompetition anti-TNF was initially used to detect antibodies to both Remicade and CT-P13. As this was not endorsed by the CHMP, the Applicant re-tested samples from both treatment arms with the same assay using tagged CT-P13. A very high concordance between the results of the two assays was demonstrated, and thus, the two assays can be considered as interchangeable. Neutralising anti-drug antibodies against CT-P13 and Remicade were measured with a competitive ligand binding assay. This method is adequately justified by available literature suggesting that B-cell epitopes of infliximab are mainly or solely located at its Fab region.

Pivotal PK Study CT-P13 1.1

Methods

Study CT-P13 1.1: randomised, double-blind, parallel-group, phase 1 study to demonstrate the equivalence with respect to the PK profile of CT-P13 and Remicade in patients with AS.

In this multicentre study, AS patients received a 2 h IV infusion of either CT-P13 (5 mg/kg) or Remicade (5 mg/kg) at Weeks 0, 2, and 6 and then once every 8 weeks up to Week 54 (Weeks 14, 22, 30, 38, 46, 54). This corresponds to 3 loading doses and 6 maintenance doses. The first 3 doses of the maintenance phase were blinded and at Week 30, the study was unblinded for reporting purposes and efficacy, PK, PD and safety endpoints were evaluated; the study remained blinded to the investigators and patients up to Week 54. Details on the study participants are given under section 2.4.3 of this report.

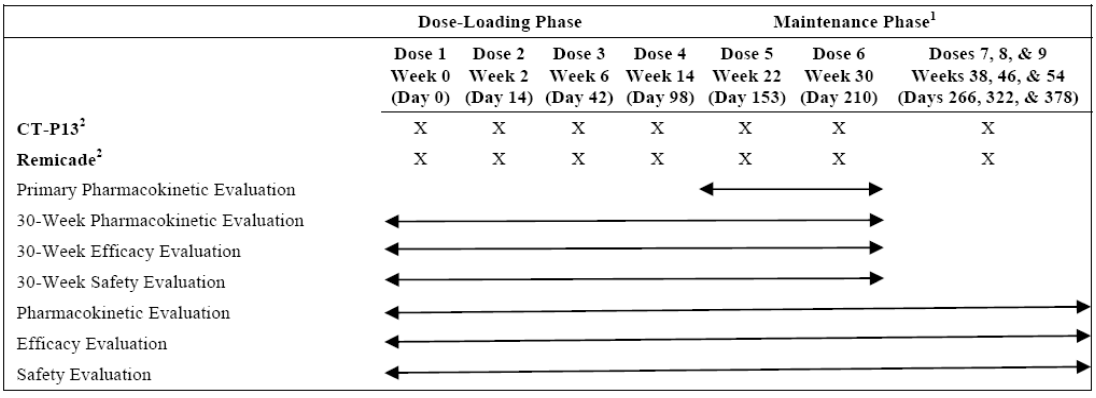


Figure 4 CT-P13 1.1 study design

Blood samples for determination of infliximab concentration were taken for each dose at three time points (pre-dose, within 15 min after the end of infusion and 1 hour after the end of infusion) with additional samples after Dose 5 (after 8 and 24 hours, then on Days 8, 15, 29, 43, 57). Blood samples for determination of antibodies were taken at screening, Weeks 14, 30, 54 and at the end of study (EOS) visit (8 weeks after the last dose).

The primary objective of this study was to demonstrate comparable PK of CT-P13 and Remicade at steady state (between Weeks 22 and 30).

The primary parameters were AUC_{τ} and C_{max} i.e. after Dose 5 (Weeks 22–30). The main secondary parameters were average concentration at steady state ($C_{av,ss}$), $C_{min,ss}$, terminal elimination half-life

($T_{1/2}$), total body clearance at steady state (CL_{ss}) and volume of distribution at steady state (V_{ss}). Other parameters were observed maximum serum concentrations (C_{max}), minimum concentration immediately before the next dose (C_{min}) and time to reach C_{max} (T_{max}) after each dose.

The PK population consisted of all patients who received at least the first 5 doses of study treatment and provided an end of infusion sample and at least 1 post-treatment PK sample. The PK population included only patients who received the study treatment to which they were randomly assigned and did not have any major protocol deviations, including a deviation of sampling time at the end of the infusion for Dose 5. Additional analyses compared the results in patients who did not develop antibodies to infliximab during the whole study period (antibody negative subset) and those who did (antibody positive subset).

Results

Subject disposition

A total of 370 patients were screened and 250 patients were randomised (125 patients in each treatment arms) and treated. At Week 30, the majority of patients in each treatment arm were continuing in the study (113 [90.4%] patients and 116 [92.8%] patients in the CT-P13 and Remicade treatment arms, respectively.

Table 14 Patient disposition in Study CT-P13 1.1

	CT-P13 5 mg/kg (N=125)	Remicade 5 mg/kg (N=125)	Total (N=250)
	Number (%) of Patients		
Screened[1]			370
Primary reason for screening failure[2]			
Inclusion/exclusion criteria not met			83
Patient withdrew consent			10
Other			20
Randomized	125 (100)	125 (100)	250 (100)
Initiated study treatment	125 (100)	125 (100)	250 (100)
Completed	0	0	0
Continuing	113 (90.4)	116 (92.8)	229 (91.6)
Discontinued	12 (9.6)	9 (7.2)	21 (8.4)
Primary reason for discontinuation			
Lack of efficacy	0	0	0
Adverse event	7 (5.6)	4 (3.2)	11 (4.4)
Life-threatening infusion-related anaphylactic reaction	0	0	0
Diabetes mellitus	0	0	0
Other adverse event	7 (5.6)	4 (3.2)	11 (4.4)
Malignancy	0	0	0
Death	0	0	0
Pregnancy	0	0	0
Patient withdrew consent	3 (2.4)	3 (2.4)	6 (2.4)
Protocol violation	0	0	0
Lost to follow-up	0	1 (0.8)	1 (0.4)
Discontinuation of the study by the sponsor	0	0	0
Investigator decision	1 (0.8)	1 (0.8)	2 (0.8)
Sponsor decision	1 (0.8)	0	1 (0.4)
Other	0	0	0

Note: The percentage of patients continuing was only displayed for analysis of the Week 30 data. The all-randomized population was used as the denominator for percentages.

1. Included screening failures and randomized patients. If a patient was screened and randomized, the treatment assignment was displayed in the "Randomized" row.
2. Included screening failures and nonrandomized patients only.

The PK population consisted of 222 patients, i.e. 112 (89.6%) for CT-P13 and 110 (88.0%) for Remicade.

Demographic characteristics

Demographic characteristics and disease activity index are summarized below. The study patients were young (mean age of 39 years) and mostly male (81%). The majority of patients (75%) had a baseline BASDAI score of <8. Demographic and baseline characteristics were similar in the two treatment arms.

Table 15 Demographic characteristics (All-randomised population)

	CT-P13 5 mg/kg (N=125)	Remicade 5 mg/kg (N=125)	Total (N=250)
Age (years)			
n	125	125	250
Mean (SD)	39.2 (12.13)	38.7 (10.48)	38.9 (11.32)
Median	38.0	38.0	38.0
Minimum, maximum	18, 69	18, 66	18, 69
Sex, no. (%)			
Male	99 (79.2)	103 (82.4)	202 (80.8)
Female	26 (20.8)	22 (17.6)	48 (19.2)
Race, no. (%)			
White	97 (77.6)	92 (73.6)	189 (75.6)
Black	0	0	0
Asian	16 (12.8)	13 (10.4)	29 (11.6)
Other	12 (9.6)	20 (16.0)	32 (12.8)
Unspecified	0	0	0
Height (cm)			
n	125	125	250
Mean (SD)	171.70 (9.63)	171.39 (8.56)	171.54 (9.10)
Median	172.0	171.0	172.0
Minimum, maximum	148, 198	147, 193	147, 198
Weight (kg)			
n	125	125	250
Mean (SD)	74.33 (15.69)	76.74 (14.30)	75.53 (15.03)
Median	72.70	76.00	73.75
Minimum, maximum	45, 120	45.5, 122.7	45, 122.7
BMI (kg/m^2)			
n	125	125	250
Mean (SD)	25.09 (4.16)	26.09 (4.29)	25.59 (4.25)
Median	24.39	25.64	25.12
Minimum, maximum	18, 38.7	17.5, 42	17.5, 42
Region, no. (%)			
European	81 (64.8)	81 (64.8)	162 (64.8)
Non-European	44 (35.2)	44 (35.2)	88 (35.2)
Baseline BASDAI score, no. (%)			
<8	92 (73.6)	95 (76.0)	187 (74.8)
≥8	33 (26.4)	30 (24.0)	63 (25.2)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index.
Note: The number of patients within each treatment group was used as the denominator for percentages.

Primary PK analysis

The primary PK parameters with statistical analyses are presented below. The 90% CIs of the geometric means ratios for both AUC_{τ} (104.10) and $C_{max,ss}$ (101.47) were within the reference range of 80%-125% indicating that the pharmacokinetic profile of infliximab is equivalent after administration of CT-P13 and Remicade.

Table 16 Analysis of primary PK parameters of infliximab (PK population)

Parameter	Treatment	n	Geometric mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
AUC_{τ} (*µg*h/mL*)	CT-P13 Remicade	111 110	32,765.51 31,475.68	104.10	93.93-115.36
$C_{max,ss}$ (*µg/mL*)	CT-P13 Remicade	112 110	146.94 144.81	101.47	94.57-108.86

The serum concentration profiles of infliximab were very similar between CT-P13 and Remicade as shown in the Figure below).

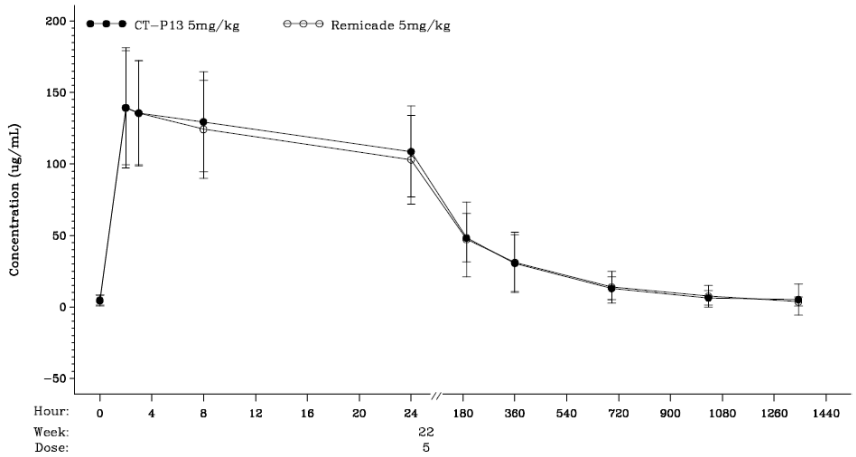


Figure 5 **Mean (±SD) serum concentrations (µg/ml) of infliximab vs time (h) by treatment for dose 5; PK population**

Secondary PK analysis

For the main secondary PK parameters after Dose 5, including half-life, clearance, volume of distribution, the 90% CIs of the geometric mean ratios also lied within the 80% - 125% limits, which further supports the similar PK behaviour of both products.

The ratio (%) of the geometric means for C_{max} ranged from 90.67 to 108.58 following Doses 1 to 9. Although this ratio was greater than 100 after most doses (i.e. higher C_{max} for CT-P13 than Remicade) the 90%CI remained within the 80 - 125% limits for all doses. A small positive correlation between C_{max} and infusion rate could be observed for both treatments but there was no statistical difference in the infusion rate of CT-P13 and Remicade. The ratio of the geometric means for C_{min} ranged from 93.89 to 113.95. Despite C_{min} being much more variable than $C_{max,}$ the 90%CI included 100% at all time points indicating no difference between the treatment arms. The median T_{max} values were also comparable in the two treatment arms.

Table 17 Geometric mean of secondary PK parameters of infliximab (PK population - all data)

Parameter	CT-P13 5 mg/kg (N = 113)		Remicade® 5 mg/kg (N = 110)		Ratio (%) of Geometric Means	90%CI of the Ratio (%)	p-value
	n	Value[b]	n	Value[b]			
Dose 1 (Week 0)							
C_{max} (µg/mL)	110	146.13	108	134.58	108.58	98.10 – 120.18	NA
C_{min} (µg/mL)	110	25.88	108	26.80	96.60	83.42 – 111.86	NA
T_{max} (h) [a]	110	2.03	108	2.09	NA	NA	0.004
Dose 2 (Week 2)							
C_{max} (µg/mL)	112	172.22	108	176.69	97.47	92.41 - 102.80	NA
C_{min} (µg/mL)	112	16.02	108	17.07	93.89	76.01 – 115.98	NA
T_{max} (h) [a]	112	2.08	108	2.08	NA	NA	0.888
Dose 3 (Week 6)							
C_{max} (µg/mL)	113	165.95	110	162.03	102.42	96.61 – 108.58	NA
C_{min} (µg/mL)	113	4.80	110	4.63	103.66	81.75 – 131.45	NA
T_{max} (h) [a]	113	2.05	110	2.08	NA	NA	0.395
Dose 4 (Week 14)							
C_{max} (µg/mL)	113	153.75	110	148.21	103.74	97.97 – 109.85	NA
C_{min} (µg/mL)	112	2.95	110	3.09	95.44	75.44 – 120.76	NA
T_{max} (h) [a]	113	2.18	110	2.08	NA	NA	0.194
Dose 5 (Week 22)							
$C_{av,ss}$ (µg/mL)	112	24.18	110	23.07	104.80	94.65 – 116.05	NA
$C_{min,ss}$ (µg/mL)	109	2.54	109	2.22	113.95	89.14 – 145.68	NA
CL_{ss} (mL/h)	112	11.38	110	12.20	93.26	84.21 – 103.27	NA
Degree of fluctuation	109	5.82	109	6.09	95.43	87.46 – 104.13	NA
$T_{1/2}$ (h)	102	277.53	98	282.96	98.08	91.03 – 105.68	NA
MRT (h)	102	328.18	98	340.08	96.50	87.69 – 106.20	NA
Swing	109	55.69	109	64.45	86.42	66.97 – 111.52	NA
V_{ss} (mL)	102	3628.84	98	3804.39	95.39	86.75 – 104.88	NA
T_{max} (h) [a]	113	3.00	110	3.00	NA	NA	0.466
Dose 6 (Week 30)							
C_{max} (µg/mL)	108	144.65	108	142.95	101.19	94.09 – 108.83	NA
C_{min} (µg/mL)	107	2.20	105	2.17	101.52	79.28 – 129.99	NA
T_{max} (h) [a]	108	2.08	108	2.19	NA	NA	0.470
Dose 7 (Week 38)							
C_{max} (µg/mL)	109	130.89	104	131.25	99.72	93.11 – 106.81	NA
C_{min} (µg/mL)	103	2.33	103	2.16	108.86	83.66 – 139.58	NA
T_{max} (h) [a]	109	2.13	104	2.08	NA	NA	0.235
Dose 8 (Week 46)							
C_{max} (µg/mL)	103	128.50	102	141.72	90.67	81.78 – 100.53	NA
C_{min} (µg/mL)	101	2.33	100	2.10	111.22	84.80 – 145.87	NA
T_{max} (h) [a]	103	2.08	102	2.07	NA	NA	0.739
Dose 9 (Week 54)							
C_{max} (µg/mL)	102	128.07	100	123.35	103.83	92.78 – 116.19	NA
T_{max} (h) [a]	102	2.08	100	2.16	NA	NA	0.449

Immunogenicity results

The results were initially presented at screening, Weeks 14 and 30. Following CHMP request, immunogenicity data were extended (up to week 54) and completed with antibody titres. Overall, 44/128 patients (34.4%) in the CT-P13 arm and 39/122 patients (32.0%) in the Remicade arm reported at least one positive ADA immunogenicity test result (i.e. seroconverted) at any time point up to week 54. Although most patients had seroconverted by week 30, 7/44 patients (16%) in the CT-P13 arm and 11/39 patients (28%) in the Remicade arm seroconverted later.

Almost all antibodies were found to be neutralising, which is expected considering the mouse (Fab)-human chimeric nature of infliximab. Comparable ADA and NAb titres were observed over time in both treatment arms. The distribution of the patients by neutralising antibody category (defined according to the tertiles of pooled data from all patients and all visits) is shown in the table below. There was a slight trend for increased antibody titres over time, which was similar in both treatment arms.

Table 18 Distribution of patients per NAb titre category (safety population)

Visit	NAb Titre Category	CT-P13 5 mg/kg (N=128)	Remicade 5 mg/kg (N=122)
	Negative	126 (98.4%)	120 (98.4%)

Screening	Low	1 (0.8%)	0
	Medium	0	0
	High	0	0
Week 14	Negative	111 (86.7%)	105 (86.1%)
	Low	3 (2.3%)	5 (4.1%)
	Medium	2 (1.6%)	2 (1.6%)
	High	5 (3.9%)	6 (4.9%)
Week 30	Negative	86 (67.2%)	87 (71.3%)
	Low	12 (9.4%)	9 (7.4%)
	Medium	11 (8.6%)	11 (9.0%)
	High	7 (5.5%)	4 (3.3%)
Week 54	Negative	84 (65.6%)	77 (63.1%)
	Low	5 (3.9%)	8 (6.6%)
	Medium	13 (10.2%)	8 (6.6%)
	High	7 (5.5%)	12 (9.8%)
End-of-study Visit	Negative	80 (62.5%)	78 (63.9%)
	Low	11 (8.6%)	4 (3.3%)
	Medium	13 (10.2%)	13 (10.7%)
	High	18 (14.1%)	18 (14.8%)

Additional analyses according to patient antibody (ADA) status were provided, which demonstrated that the presence of antibodies significantly reduced systemic exposure to infliximab by increasing its clearance and decreasing its half-life, volume of distribution, and serum concentrations. However, the magnitude of the impact of ADAs on the PK parameters was comparable between both treatments as reflected in the tables below.

Table 19 Analysis of primary PK parameters of infliximab – Dose 5 (PK population excluding aberrant values)

Parameter	Treatment	N	Geometric mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
Antibody-negative subset					
AUC_T *(h*µg/mL)*	CT-P13 Remicade	80 76	37,725.49 37,220.95	101.36	92.48–111.09
$C_{max,ss}$ *(µg/mL)*	CT-P13 Remicade	81 76	152.74 147.84	103.32	95.39–111.91
Antibody-positive subset					
AUC_T *(h*µg/mL)*	CT-P13 Remicade	31 34	22,821.56 21,313.74	107.07	86.95–131.86
$C_{max,ss}$ *(µg/mL)*	CT-P13 Remicade	32 34	133.92 136.61	98.04	85.07–112.98

Table 20 Descriptive statistics of secondary PK parameters of infliximab – Dose 5 (PK population – all data)

Parameter	ADA subset	n	CT-P13 Geometric Mean (CV)	n	Remicade® Geometric Mean (CV)
$C_{av,ss}$ (µg/mL)	Negative	83	27.59 (27.2)	83	27.35 (37.9)
	Positive	27	16.37 (41.0)	24	13.66 (41.1)
CL_{ss} (mL/hr)	Negative	83	10.10 (31.7)	83	10.33 (33.6)
	Positive	27	16.17 (87.5)	24	20.69 (55.8)
$C_{min, ss}$ (ug/mL)	Negative	83	3.70 (120.5)	83	3.18 (71.3)
	Positive	26	0.76 (427.2)	24	0.59 (38.2)
Degree of Fluctuation	Negative	83	5.34 (28.4)	83	5.31 (35.2)
	Positive	26	7.63 (31.2)	24	10.01 (39.5)
$T_{1/2}$ (hr)	Negative	78	310.63 (27.0)	80	304.65 (28.8)
	Positive	22	193.19 (10.7)	15	181.79 (7.9)
MRT (hr)	Negative	78	377.81 (31.4)	80	373.92 (31.7)
	Positive	22	212.35 (25.0)	15	192.81 (22.3)
Swing	Negative	83	39.79 (116.7)	83	45.71 (111.9)
	Positive	26	162.94 (50.7)	24	233.36 (33.9)
T_{max} (hr)	Negative	83	3.00 (2.00, 359.08)	83	2.25 (1.98, 168.00)
	Positive	27	3.00 (2.00, 168.00)	24	3.00 (2.00, 24.17)
V_{ss} (mL)	Negative	78	3828.01 (28.6)	80	3809.82 (33.9)
	Positive	22	3136.49 (32.4)	15	3223.11 (28.4)

Supportive PK data

Study CT-P13 3.1

Methods

Supportive PK data were generated from the pivotal efficacy trial, which was designed to show therapeutic equivalence of CT-P13 and Remicade. PK parameters were included as secondary endpoints. Blood samples were taken at each dose as in the pivotal PK study (without additional sampling after Dose 5) and the same PK parameters were estimated. The study treatment was the same as in the pivotal PK trial except for the dose, 3 mg/kg. In addition, MTX (12.5 to 25 mg/week oral or parenteral) with folate was co-administered.

Results

PK results

The geometric means of C_{max} and C_{min} appeared similar after the infusions of CT-P13 and Remicade in the PK population as reflected below.

Table 21 Geometric mean of PK parameters Dose 1 – 9 (PK population – all data)

Parameter	CT-P13 3 mg/kg (N = 290)		Remicade® 3 mg/kg (N = 288)		Ratio (%) of Geometric Means	90%CI of the Ratio (%)	p-value
	n	value	n	value			
Dose 1 (Week 0)							
C_{max} (µg/mL)	290	89.87	285	88.53	101.51	96.20 – 107.11	NA
C_{min} (µg/mL)	286	16.40	282	17.16	95.56	85.61 – 106.66	NA
T_{max} (h) [a]	290	3.00	285	2.12	NA	NA	0.007
Dose 2 (Week 2)							
C_{max} (µg/mL)	286	112.16	285	104.44	107.40	102.65 – 112.36	NA
C_{min} (µg/mL)	279	6.37	279	7.59	83.87	70.75 – 99.43	NA
T_{max} (h) [a]	286	2.17	285	3.00	NA	NA	0.720
Dose 3 (Week 6)							
C_{max} (µg/mL)	276	98.68	277	96.28	102.50	95.97 – 109.46	NA
C_{min} (µg/mL)	267	1.52	265	1.49	101.76	86.77 – 119.34	NA
T_{max} (h) [a]	276	2.25	277	2.92	NA	NA	0.728
Dose 4 (Week 14)							
C_{max} (µg/mL)	267	90.37	263	86.16	104.89	98.36 – 111.85	NA
C_{min} (µg/mL)	259	1.04	252	1.09	95.38	83.34 – 109.16	NA
T_{max} (h) [a]	267	3.00	263	2.37	NA	NA	0.305
Dose 5 (Week 22)							
C_{max} (µg/mL)	256	90.88	254	84.11	108.04	100.72 – 115.89	NA
C_{min} (µg/mL)	239	1.00	243	1.04	95.84	82.01 – 112.01	NA
$C_{av,ss}$ (µg/mL)	239	47.33	243	43.38	109.10	101.72 – 117.02	NA
PTF	239	1.82	242	1.89	96.03	90.54 – 101.84	NA
T_{max} (h) [a]	256	3.00	254	2.21	NA	NA	0.011
Dose 6 (Week 30)							
C_{max} (µg/mL)	242	81.80	245	82.07	99.67	91.98 – 108.00	NA
C_{min} (µg/mL)	233	0.86	233	0.89	97.48	85.33 – 111.35	NA
T_{max} (h) [a]	242	2.08	245	2.18	NA	NA	0.371
Dose 7 (Week 38)							
C_{max} (µg/mL)	241	79.06	237	78.75	100.39	91.48 – 110.17	NA
C_{min} (µg/mL)	234	0.89	228	0.91	97.71	83.59 – 114.21	NA
T_{max} (h) [a]	241	2.08	237	2.17	NA	NA	0.245
Dose 8 (Week 46)							
C_{max} (µg/mL)	235	73.87	231	66.57	110.97	98.21 – 125.38	NA
C_{min} (µg/mL)	228	0.93	219	0.97	95.38	81.10 – 112.18	NA
T_{max} (h) [a]	235	2.08	231	2.08	NA	NA	0.667
Dose 9 (Week 54)							
C_{max} (µg/mL)	227	66.08	214	60.26	109.66	94.49 – 127.26	NA
T_{max} (h) [a]	227	2.08	214	2.08	NA	NA	0.443

Immunogenicity results

Overall, 168/302 patients (55.6%) in the CT-P13 arm and 163/300 patients (54.3%) in the Remicade arm seroconverted up to week 54. No marked differences in the distribution of the patients by neutralising antibody category were observed between the two treatment arms.

Table 22 Distribution of patients per NAb titre category (safety population)

Visit	NAb Titre Category	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=300)
Screening	Negative	299 (99.0%)	295 (98.3%)
	Low	1 (0.3%)	2 (0.7%)
	Medium	0	0
	High	1 (0.3%)	1 (0.3%)
Week 14	Negative	200 (66.2%)	201 (67.0%)
	Low	14 (4.6%)	13 (4.3%)
	Medium	29 (9.6%)	29 (9.7%)
	High	28 (9.3%)	26 (8.7%)

Visit	NAb Titre Category	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=300)
Week 30	Negative	129 (42.7%)	134 (44.7%)
	Low	28 (9.3%)	38 (12.7%)
	Medium	46 (15.2%)	31 (10.3%)
	High	49 (16.2%)	50 (16.7%)
Week 54	Negative	113 (37.4%)	114 (38.0%)
	Low	27 (8.9%)	30 (10.0%)
	Medium	38 (12.6%)	36 (12.0%)
	High	59 (19.5%)	38 (12.7%)
End-of-study Visit	Negative	113 (37.4%)	121 (40.3%)
	Low	39 (12.9%)	44 (14.7%)
	Medium	49 (16.2%)	38 (12.7%)
	High	69 (22.8%)	66 (22.0%)

As previously seen in study CT-P13 1.1, the development of ADA antibodies had a significant impact on peak and trough concentrations, which were lower in the antibody-positive subset of patients compared to the antibody-negative subset. This impact was similar in both treatment arms.

Study CT-P13 1.2

Study CT-P13 1.2 is a randomised, double-blind, parallel-group, Phase I study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis.

Methods

The study was designed to provide preliminary data on PK, PD, efficacy and safety of multiple doses of CT-P13 compared to Remicade (3 mg/kg) administered by a 2 h IV infusion when co-administered with MTX (between 12.5 to 25 mg/week, oral dose) and folic acid (≥5 mg/kg/week, oral dose) in patients with active RA. The primary objective was to demonstrate comparable C_{max} and PK profiles between CT-P13 and Remicade in patients with active RA at Weeks 0, 2 and 6.

The total duration was up to 112 week. At Week 6 the study was unblinded for reporting purposes and PK endpoints and preliminary safety endpoints were evaluated; the study remained blinded to the investigators and patients up to Week 54. At Week 30, secondary endpoints, i.e. efficacy, PK, PD, and safety were assessed. This study is on-going. The patient selection criteria were similar to those of Study CT-P13 3.1.

Results

In total 19 patients were randomised: 9 to CT-P13 and 10 to Remicade. Values of C_{max} at Doses 1, 2 and 3 (Weeks 0, 2 and 6) were comparable. Mean C_{max} for the CT-P13 arm ranged from 76.1 to 84.8 µg/mL and mean C_{max} for the Remicade arm from 64.6 to 78.3 µg/mL.

This study was also used to evaluate the fate of the infliximab C-terminal lysine variants. Blood samples were taken from 8 patients (5 treated with CT-P13 and 3 treated with Remicade) immediately and 1 h post infusion following Doses 1, 3 and 6. Samples were pooled for each time point and assayed for C-terminal lysine content. C-terminal lysine was not detected in most samples with only minor levels being detected in samples from patients treated with CT-P13 Dose 1, namely 3.1% and 0.4%

immediately and 1 h post infusion, respectively. This indicates rapid cleavage of the C-terminal lysine residues in blood following administration.

Relevance of the PK results to all approved indications

Remicade is approved in several indications in inflammatory diseases, including RA, AS, PsA, adults and paediatric CD, adults and paediatric UC and Ps. Study CT-P13 1.1 designed to demonstrate PK equivalence of CT-P13 and Remicade was conducted in patients with AS. In accordance with the guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), the primary objective of PK studies performed to support a MAA for a similar biological medicinal product is to show comparability in PK of the biosimilar with the reference product in a sufficiently sensitive and homogeneous population. Patients with AS were considered as a sensitive population, because these patients are generally young, otherwise healthy and not receiving concomitant medication such as MTX, which has been shown to have an effect on anti-infliximab antibody status and thus on infliximab clearance (Xu et al. 2008). Furthermore, the available data and published literature on Remicade indicate that there are no significant differences in PK profiles for Remicade in patients with RA, adult and paediatric CD, and Ps (Klotz et al. 2007, Nestorov 2005) and there are no data to indicate that the PK profile in these three indications differ from the PK profile in AS patients. Also, infliximab serum levels in paediatric patients with CD were similar to those in adult CD patients.

A recent retrospective analysis of data from 2 phase III clinical trials in CD patients found that age did not influence infliximab PK in the range of 6 – 76 years (Fasanmade et al. 2011). Although the balance of data report similarities for infliximab PK profiles in different patient populations, it is noted that some studies report differences but these are attributed to differences in immunological responses in different populations. For example, the systemic clearance of infliximab was reported to be similar in patients with AS and RA (0.27 L/day), but lower than in patients with CD (0.36 L/day). In this PK study, it was concluded that of all the covariates evaluated, it was anti-infliximab antibody status that had the most significant influence on infliximab clearance being associated with accelerated clearance (Xu et al. 2008). Differences in PK were also reported between patients receiving co-administration of MTX and patients who did not receive MTX. In an interaction study, the plasma concentrations of infliximab were found to be slightly increased by MTX.

Absorption

CT-P13 is intended for IV administration and consequently, bioavailability studies are not needed.

Distribution

The mean V_{ss} for CT-P13 was calculated to be 3788.85 mL ~3.8 L, similar to that of the reference product Remicade (median V_{ss} of 3.0-4.1 L in the Remicade SmPC) indicating that infliximab is predominantly distributed within the vascular compartment.

Elimination

There are no specific studies regarding the metabolism or excretion of infliximab in humans. It is expected that infliximab is eliminated in a similar manner as native antibodies.

Dose proportionality

Dose-proportionality was not evaluated. In the clinical studies, the study products were administered at the recommended therapeutic dose, i.e. 5 mg/kg in AS and 3 mg/kg in RA.

Special populations

No studies were performed in patients with hepatic impairment and in patients with renal impairment as these are not required for a similar biological medicinal product.

Pharmacokinetic interaction studies

No PK interaction studies were performed as these are not required for a similar biological medicinal product.

2.4.3. Pharmacodynamics

CT-P13 contains infliximab, a chimeric (i.e. contains human constant and murine variable regions) immunoglobin G1 (IgG1) monoclonal antibody (mAb) that binds with high affinity to the human tumour necrosis factor alpha (TNFα).

Mechanism of action

Most studies on the mechanisms of action of TNF antagonists have been performed in RA. A few studies have been conducted in other rheumatic diseases, such as AS, JIA or PsA. Initial data suggest that the effects of TNF blockade on synovial inflammation are comparable in different forms of arthritis. Biopsy studies from patients with RA, CD and Ps suggest that TNFα antagonists share many common mechanisms of action across these diseases (Tracey et al. 2008).

Infliximab acts by binding to and neutralising soluble TNFα (sTNF) and membrane bound TNFα (tmTNF), preventing TNF from binding to its receptor (TNFR) and inducing associated cellular functions. When TNF antagonists bind to tmTNF, they inhibit its binding to the TNF receptor (TNFR) on the surface of cells such as human T-cells and rheumatoid synovial macrophages, and in lamina propria bowel wall T cells in CD. They may also induce a direct effect upon the tmTNF-bearing cells such as apoptosis, cytokine suppression, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.

As part of the nonclinical development programme as well as the pharmaceutical comparability exercise of CT-P13, an extensive battery of *in vitro* tests comparing CT-P13 to Remicade was conducted. These tests covered investigations of the binding affinity of CT-P13 and Remicade for human TNFα, for soluble human TNFα in trimeric and monomeric forms, for tmTNF-Jurkat cells, Fcγ receptors (FcγRI, FcγRII, FcRn and FcγRIIIa), and to C1q, as well as cross reactivity to a panel of 40 human tissues in a GLP-compliant immunohistochemical study. All these tests found that CT-P13 and Remicade display comparable activity.

Primary and secondary pharmacology

No direct pharmacodynamic effects can be attributed to anti-TNFs in patients. The pharmacodynamic endpoints studied in the pivotal efficacy trial (CT-P13 3.1) are markers of disease activity and do not have a clear relationship to therapeutic effect. These markers included C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and antibodies against cyclic citrullinated peptide (anti-CCP) concentration. These PD parameters were discussed as part of the scientific advice procedure (EMA/CHMP/SAWP/788791/2009). Statistical analyses (ANCOVA) of anti-CCP, CRP, ESR, IgA RF, IgG RF, and IgM RF are summarised below for the PD population.

Table 23 Summary of PD parameters (PD population)

Visit Treatment Arm	N	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
Concentration of anti-CCP (*IU/mL*)				

Visit Treatment Arm	N	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
Baseline				
CT-P13	*264*	*190.06*		
Remicade	*259*	*201.62*		
Week 14				
CT-P13	244	191.13 (5.670)	-1.61	(-17.35, 14.13)
Remicade	235	192.74 (5.777)		
Week 30				
CT-P13	222	192.94 (5.898)	19.68	(3.46, 35.90)
Remicade	219	173.27 (5.939)		
Concentration of CRP (*mg/dL*)				
Baseline				
CT-P13	*292*	*1.90*		
Remicade	*290*	*1.89*		
Week 14				
CT-P13	270	1.25 (0.130)	0.20	(-0.16, 0.56)
Remicade	272	1.06 (0.130)		
Week 30				
CT-P13	251	1.11 (0.097)	0.08	(-0.19, 0.34)
Remicade	253	1.04 (0.097)		
ESR (*mm/h*)				
Baseline				
CT-P13	*291*	*47.0*		
Remicade	*290*	*48.5*		
Week 14				
CT-P13	271	33.73 (1.096)	2.62	(-0.40, 5.64)
Remicade	272	31.11 (1.098)		
Week 30				
CT-P13	250	31.51 (1.222)	-0.51	(-3.87, 2.84)
Remicade	253	32.03 (1.220)		
Concentration of IgA RF (*IU/mL*)				
Baseline				
CT-P13	*284*	*55.83*		
Remicade	*281*	*65.39*		
Week 14				
CT-P13	262	43.69 (2.693)	1.70	(-5.74, 9.13)
Remicade	257	41.99 (2.735)		
Week 30				
CT-P13	238	35.96 (3.072)	1.10	(-7.29, 9.50)
Remicade	239	34.86 (3.079)		
Concentration of IgG RF (*IU/mL*)				
Baseline				
CT-P13	*284*	*68.35*		
Remicade	*281*	*66.68*		
Week 14				
CT-P13	262	39.73 (2.332)	6.68	(0.26, 13.10)
Remicade	257	33.05 (2.363)		
Week 30				
CT-P13	238	33.52 (2.351)	3.43	(-2.98, 9.84)
Remicade	239	30.09 (2.352)		
Concentration of IgM RF (*IU/mL*)				
Baseline				
CT-P13	*284*	*122.58*		
Remicade	*281*	*128.38*		

Visit Treatment Arm	N	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 14				
CT-P13	262	91.05 (3.708)	4.69	(-5.53, 14.91)
Remicade	257	86.35 (3.762)		
Week 30				
CT-P13	238	84.60 (3.907)	1.70	(-8.96, 12.35)
Remicade	239	82.91 (3.908)		

Given the distribution of these parameters, their evolution is better described by the median changes from baseline, which appeared quite similar in both treatment arms. Although these parameters cannot be considered as markers of the therapeutic response, their evolution suggests a similar decrease in the disease activity under treatment with the test or reference products.

There was no change in anti-CCP levels up to Week 30; the median change from baseline was zero in both treatment arms. Baseline CRP levels ranged between 0.02 and 20.8 mg/dL with a median of 1.08 and 1.10 in the CT-P13 and Remicade arms, respectively. A rapid decrease was seen in both treatment arms with a median change from baseline of -0.4 mg/dL at Week 30. Likewise, a rapid decline in ESR was observed after the first dose, which remained more or less unchanged after the second dose up to Week 30 (median change of -16.0 and -17.0 mm/h in the CT-P13 and Remicade arms, respectively).

In general, individual changes in RF were highly variable in both directions. For IgA RF, the median change was marginal at Week 30 (-2.6 and -2.0 IU/mL in the CT-P13 and Remicade arms, respectively). A progressive decrease was observed for IgG RF and IgM RF; the median decrease at Week 30 was similar in both treatment arms: -11. 2 and -9.1 IU/mL in the CT-P13 and Remicade arms, respectively, for IgG RF; -16. 1 and -15.9 IU/mL in the CT-P13 and Remicade arms, respectively, for IgM RF.

In term of secondary pharmacology, the tolerability of CT-P13 and Remicade infusions was monitored. Infusion reactions are described in the adverse event sections. There were no differences between the two treatments with regard to the pulse rate, blood pressure or ventilation rate.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The design of the large comparative multiple dose trial conducted in AS patients (Study CT-P13 1.1) was endorsed as the pivotal PK trial by a CHMP scientific advice. Due to the long half-life and immunogenicity of infliximab, a parallel group design was considered appropriate and allowed the comparison of the PK and immunogenicity of CT-P13 and Remicade in a sensitive patient population as already mentioned. The assay formats employed by the Applicant for the measurement of infliximab and anti-infliximab antibodies were considered acceptable.

A total of 250 patients were randomised and the PK population consisted of 222 patients (112 for CT-P13 and 110 for Remicade). The co-primary PK endpoints were set as AUC_T and $C_{max,ss}$ between Weeks 22 and 30. The 90% CIs of the geometric means ratios for both AUC_T and $C_{max,ss}$ lied between 93% and 116%, well contained within the standard bioequivalence interval of 80%-125%; this demonstrates that the PK of infliximab is equivalent between CT-P13 and Remicade at the dose of 5 mg/kg. Furthermore, equivalent PK was also shown in the antibody-negative subset of the patient population. The main secondary PK endpoints such as $T_{max,}$ $C_{min,ss}$, $T_{½}$, CL_{ss}, V_{ss} between Weeks 22 and 30, as well as C_{max} and C_{min} after the 9 treatment doses, were also comparable in the CT-P13 and Remicade treatment arms in the PK population and its antibody-negative subset, providing further evidence of a similar PK behaviour.

Supportive PK data were generated in the pivotal study CT-P13 3.1 providing estimates of C_{min}, C_{max}, and T_{max} in RA patients. The PK population consisted of 578 patients, i.e. 290 for CT-P13 and 288 for Remicade. Generally, peak and trough levels measured after the 9 treatment doses of 3 mg/kg were similar between CT-P13 and Remicade arms.

Infliximab is a chimeric monoclonal antibody known to be highly immunogenic with consequences on its PK, safety, and efficacy. The immunogenicity profile of CT-P13 has been well characterised in the two clinical studies CT-P13 1.1 and CT-P13 3.1. Over the 54-week treatment period, a generally similar proportion of patients developed anti-infliximab antibodies (ADA) in the two treatment arms: 34.4% (CT-P13) vs. 32.0% (Remicade) in the AS study CT-P13 1.1 and 55.6% (CT-P13) vs. 54.3% (Remicade) in the RA study CT-P13 3.1. Essentially, all these antibodies were found to be neutralising (Nabs). Antibody titres of ADA and Nabs increased slightly over time up to 30 weeks and no marked differences were observed between the two treatment arms. As expected, these antibodies significantly reduced the systemic exposure to infliximab in both clinical studies but their impact appeared generally comparable in the two treatment arms.

Based on the review of the literature provided by the Applicant, there is no evidence of notable differences in the PK of infliximab across its various indications. With the two studies in AS and RA, the Applicant has covered the two recommended doses of infliximab (3 and 5 mg/kg). Moreover, data have been generated both in monotherapy and in combination with MTX. Therefore, from a PK perspective, it is considered that sufficient data are available to support their extrapolation to all indications of Remicade. In addition, the patient populations selected (AS and RA) are considered sensitive to evaluate immunogenicity; even in combination with MTX, a high level of immune response was demonstrated.

No interaction studies have been performed as this is not a requirement for a similar biological medicinal product. Concomitant use of MTX and other immunomodulators may reduce the formation of antibodies against infliximab and increase the plasma concentrations of infliximab. Corticosteroids do not appear to affect the PK of infliximab to a clinically relevant extent. The combination of CT-P13 with other biological therapeutics used to treat the same conditions as CT-P13, including anakinra and abatacept, is not recommended

Pharmacodynamics

In the absence of clinically relevant marker of therapeutic activity, several markers of inflammation or disease activity (RF, anti-CCP, ESR, and CRP) were measured as PD parameters during the pivotal efficacy trial CT-P13 3.1. Great variability was observed in individual changes, but overall, their evolution suggested a similar decrease in the disease activity under treatment with CT-P13 or Remicade.

2.4.5. Conclusions on clinical pharmacology

The pivotal PK trial (Study CT-P13 1.1) demonstrated that CT-P13 and Remicade exhibit a similar PK profile over the first 30 weeks of treatment. In particular, equivalence of systemic exposure to infliximab (AUC_T and $C_{max,ss}$) was established at steady state. These results are supported by PK data collected in RA patients (Study CT-P13 3.1). Overall, the results are consistent across both clinical studies and provide a robust evidence for a similar PK profile between CT-P13 and Remicade.

Studies CT-P13 1.1 in AS and 3.1 in RA covered the two recommended doses of infliximab (3 and 5 mg/kg), two different patient populations (age, co-morbidities) and two different types of administration (monotherapy and combination with methotrexate). Therefore, from a PK perspective, the data adequately support their extrapolation to all other indications of Remicade. Likewise, the immunogenicity profile of CT-P13, which has been well characterised in the two clinical studies, appeared comparable to that of Remicade and can be extrapolated to all other indications of the reference product.

2.5. Clinical efficacy

The pivotal efficacy trial (Study CT-P13 3.1) evaluated the therapeutic equivalence of CT-P13 compared to Remicade in patients with active RA. Supportive efficacy data were collected in the pivotal PK trial (Study CT-P13 1.1) conducted in AS patients.

2.5.1. Dose-response study

No dose-response studies have been performed. As this application relates to a biosimilar product there is no requirement for dose-response studies. The proposed dosing regimens for CT-P13 are identical to those approved for Remicade. Depending on the indication, a loading dose regimen of 3 or 5 mg/kg at 0, 2 and 6 weeks may be followed by a maintenance dose regimen of the same dose every 6 or 8 weeks.

2.5.2. Main study

Study CT-P13 3.1: Randomised, double blind, multicentre, parallel group, Phase 3 study to demonstrate equivalence in efficacy and safety of CT-P13 compared with Remicade when co-administrated with methotrexate in patients with active RA.

Methods

Study Participants

Main inclusion criteria

- Male or female aged 18 to 75 years old;
- Diagnosis of active RA according to the revised 1987 ACR classification criteria for at least 1 year prior to screening;
- Active disease as defined by the presence of 6 or more swollen joints, 6 or more tender joints, and at least 2 of the following: morning stiffness lasting at least 45 minutes, an erythrocyte sedimentation rate (ESR) greater than 28 mm/h, and a serum C-reactive protein (CRP) concentration greater than 2.0 mg/dL;
- Completion of at least 3 months of treatment of oral or parenteral dosing with MTX between 12.5 to 25 mg/week and on a stable dose for at least 4 weeks prior to screening.

Main exclusion criteria

- Previous administration of a biological agent for the treatment of RA;
- Allergies to any of the excipients of infliximab or any other murine and human proteins as well as hypersensitivity to immunoglobulin product;
- History of hepatitis B, Hepatitis C, or infection with human immunodeficiency virus-1 or -2 or positive result to the screening test for those infections;
- Current diagnosis of TB or other severe chronic infection or a past diagnosis without sufficient documentation of complete resolution following treatment;
- Other inflammatory or rheumatic diseases.

Prohibited concomitant medications

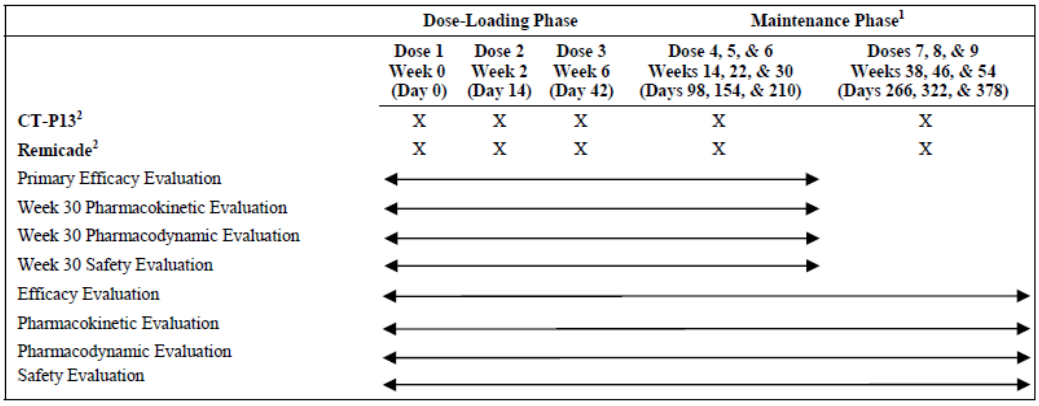
- Corticosteroids, except oral glucocorticoids of maximum equivalent daily dose of 10 mg of prednisolone within 4 weeks prior to screening;

- DMARDs including hydroxychloroquine, chloroquine, methotrexate, or sulfasalazine, within 4 weeks prior to screening;
- Alkylating agents within 12 months prior to screening;
- Live or live-attenuated vaccine within 8 weeks of screening;
- Any biological agents for the treatment of RA.

Treatments

Patients received a 2-hour IV infusion of either CT-P13 (3 mg/kg) or Remicade (3 mg/kg) at Weeks 0, 2, and 6 and then once every 8 weeks up to 54 weeks. CT-P13 and Remicade were co-administered with MTX, as an oral or parenteral dose of 12.5 - 25 mg/week, and folic acid, as an oral dose ≥5 mg/week. Patients were required to be on a stable dose of MTX for at least 4 weeks prior to screening, which was maintained from the beginning to the end of the study.

Patients were randomly assigned in a 1:1 ratio to receive either CT-P13 or Remicade. The duration of the study was up to 68 weeks and consisted of 4 treatment periods including screening (up to 6 weeks), dose-loading phase (6 weeks), maintenance phase (48 weeks), and the end of study period (8 weeks after the last dose).



1. Following Dose 3, further doses could be administered every 8 weeks up to Week 54 continuing with assigned treatment.
2. A dose visit window of ±3 days is allowed up to and including Dose 6; a dose visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.

Figure 6 CT-P13 3.1 study design

Objectives

The primary objective of this study was to demonstrate that CT-P13 was equivalent to Remicade up to Week 30, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20).

The secondary objectives of this study were to evaluate long-term efficacy, pharmacokinetics, pharmacodynamics, and overall safety of CT-P13 in comparison with Remicade up to Week 54.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients achieving clinical response in accordance to the ACR criteria of 20% improvement (ACR20) at Week 30.

Main secondary efficacy endpoints:

- Individual components of the ACR criteria, comparison with baseline at Weeks 14 and 30;
- ACR20 at Week 14; ACR50 and ACR70 at Weeks 14 and 30;

- Mean decrease in disease activity measured by DAS28 (using both ESR and CRP) at Week 14 and 30;
- Proportion of patients with a good response, defined according to the EULAR response criteria, at Week 14 and 30;
- SDAI and CDAI at Weeks 14 and 30;
- SF-36 at Weeks 14 and 30.

Sample size

A total of 584 male or female patients were to be enrolled in the study. Therapeutic equivalence to Remicade in the all-randomised population was based on expected responder rates of 50% in the test and control groups. Specifying a 2-sided alpha level of 0.05, power of 80%, and a 2-sided equivalence margin of 15% would require 468 patients to be included in the per-protocol population for the final analysis. Assuming that 20% of patients would be excluded from the per-protocol (PP) population would require 584 patients in total to be randomly assigned to treatment.

Based on a meta-analysis of historical data with Remicade, in particular the ATTRACT trial, an equivalence margin of 15% was shown to ensure superiority over placebo. Although the proposed margin of ±15% could be considered clinically relevant, it was accepted by the CHMP in the context of a biosimilarity exercise, since it is also based on physicochemical, biological, and PK comparisons.

Randomisation

On Day 0, Week 0, patients were randomly assigned in a 1:1 ratio to receive either CT-P13 or Remicade using an interactive voice response system (IVRS) with stratification by geographic region and CRP (> 2.0 vs. ≤ 2.0 mg/dL).

Blinding (masking)

This study was patient, investigator and sponsor-blinded. At Week 30, the study was unblinded for reporting purposes and efficacy, PK, PD and safety endpoints were evaluated; the study remained blinded to the investigators and patients up to Week 54.

Statistical methods

Efficacy analyses sets

The PP population consisted of all randomised patients who did not have major protocol deviations, i.e. who fully complied with the inclusion and exclusion criteria, had received all doses of study treatment up to Week 30, did not discontinue or reduce their MTX dose below 12.5 mg/week for more than 2 consecutive weeks up to Week 30 because of toxicity or non-compliance, and had an ACR assessment at Week 30.

The all-randomised population consisted of all patients enrolled and randomly assigned to receive a dose of either of the study treatments, regardless of whether or not any study treatment dosing was completed. Eleven patients (7 patients and 4 patients in the CT-P13 and Remicade treatment arms, respectively) from a potentially fraudulent study centre, which had been closed due to suspected misconduct, were excluded. After unblinding, a sensitivity analysis was performed with inclusion of these patients.

Definition of ACR response

A patient was defined as a responder according to ACR20 criteria if the following was fulfilled:

- A decrease of at least 20% in the number of tender joints
- A decrease of at least 20% in the number of swollen joints and

- At least a 20% improvement in 3 of the following: patient assessment of pain on VAS; patient global assessment of disease status (VAS); physician global assessment of disease status (VAS); health assessment questionnaire estimate of physical ability; serum CRP concentration or ESR.

In addition, patients were considered non-responders if they had discontinued the study, had missing or incomplete data for the evaluation of ACR20, had protocol-prohibited medication or changes in medication, or required a surgical joint procedure during the study.

Statistical tests

Primary analysis

The proportion of patients achieving ACR20 clinical response at Week 30 was analysed by the exact binominal approach, calculating a point estimate and 95% CI for the difference in proportion between the 2 treatment arms. Therapeutic equivalence was concluded if 95% CI for the treatment difference was entirely within -15% to 15%. As this method did not allow for stratification, a sensitivity analysis was performed on the primary endpoint, utilizing a logistic regression model, with randomised treatment arm as a fixed effect, and region and CRP category as covariates. The primary efficacy analyses were performed on both the all-randomised and PP populations.

Secondary analyses

The secondary efficacy analyses were only performed in the PP population. Descriptive statistics for actual and change from baseline for the individual components of ACR criteria were calculated by treatment and study visit. For the comparison of ACR20 at Week 14 and ACR50 and ACR 70 at Weeks 14 and 30 between CT-P13 and Remicade, proportions were analysed by exact binominal approach. A sensitivity analysis was performed similar to that described above for analysis of the primary endpoint. An analysis of covariance (ANCOVA) was performed at each of the efficacy visits with DAS28 as response, treatment arm as fixed effect and baseline DAS28 score, region and CRP category as covariates. A point estimate and 95% CI for the treatment difference were provided. The EULAR response criteria were analysed using a proportional odds model stratified by region and CRP, calculating an odds ratio with 95% CI for the difference in response between the 2 treatment arms. Descriptive statistics were presented for other secondary efficacy data.

Results

Participant flow

Of 1,077 patients screened, 606 were randomised to either CT-P13 (N=302) or Remicade (N=304). In total 300 (99.3%) patients and 302 (99.3%) patients in the CT-P13 and Remicade treatment arms, respectively, initiated study treatment. A similar proportion of patients in each treatment arm discontinued the study by Week 30: 49 [16.2%] patients and 46 [15.1%] patients in the CT-P13 and Remicade treatment arms, respectively. The most frequently reported reasons for discontinuation from the study were adverse events (7.3% and 5.9%, respectively) and withdrawal of consent (3.6% and 5.3%, respectively). At Week 30, the PP population comprised a total of 499 patients, with 248/302 (82.1%) randomised to CT-P13 and 251/304 (82.6%) to Remicade.

Table 24 Patient disposition at Week 30 (All-randomised population)

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=304)	Total (N=606)
	Number (%) of Patients		
Screened[1]			1077
Primary reason for screening failure[2]			
Inclusion/exclusion criteria not met			367
Patient withdrew consent			19
Other			74
Randomized	302 (100)	304 (100)	606 (100)
Initiated study treatment	300 (99.3)	302 (99.3)	602 (99.3)
Continuing	253 (83.8)	258 (84.9)	511 (84.3)
Discontinued	49 (16.2)	46 (15.1)	95 (15.7)
Primary reason for discontinuation			
Lack of efficacy	6 (2.0)	0	6 (1.0)
Adverse event	22 (7.3)	18 (5.9)	40 (6.6)
Malignancy	0	2 (0.7)	2 (0.3)
Patient withdrew consent	11 (3.6)	16 (5.3)	27 (4.5)
Protocol violation	2 (0.7)	2 (0.7)	4 (0.7)
Sponsor decision	7 (2.3)	6 (2.0)	13 (2.1)
Other	1 (0.3)	2 (0.7)	3 (0.5)

Note: The percentage of patients continuing was only displayed for analysis of the Week 30 data. The all-randomized population was used as the denominator for percentages.

1. Included screening failures and randomized patients. If a patient was screened and randomized, the treatment assignment was displayed in the "Randomized" row.
2. Included screening failures and nonrandomized patients only.

Fewer patients discontinued the study by Week 54 in the CT-P13 arm (69; 22.8%) than in the Remicade arm (82; 27.0%); thus, 233 patients (77.2%) treated with CT-P13 completed the trial versus 222 patients (73.0%) treated with Remicade. The most frequently reported reasons for discontinuation from the study by Week 54 were adverse events (31[10.8%] patients and 41 [13.5%] patients in the CT-P13 and Remicade treatment arms, respectively) and withdrawal of consent (16 [5.3%] patients and 21 [6.9%] patients in the CT-P13 and Remicade treatment arms, respectively). Lack of efficacy was reported in 10 patients treated with CT-P13 and 6 patients treated with Remicade.

Recruitment

The first subject was randomised on 13 December 2010 and the Week 30 Cut-Off Date was on 20 December 2011. A total of 100 study centres across 19 countries worldwide enrolled patients.

Conduct of the study

The study protocol was amended 4 times mostly to clarify details of patient selection criteria. The CHMP considered that these amendments have not impacted the outcome of the study.

The most frequently reported major protocol deviations were patients who did not receive all doses of study treatment up to Week 30 (48 [15.9%] patients and 44 [14.5%] patients in the CT-P13 and Remicade treatment arms, respectively) and patients who did not have an ACR assessment at Week 30 (45 [14.9%] patients and 43 [14.1%] patients in the CT-P13 and Remicade treatment arms, respectively).

Table 25 Protocol deviations (All-randomised population)

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=304)	Total (N=606)	Excluded Populations[1]
	Number (%) of Patients			
Misrandomizations	0	1 (0.3)	1 (0.2)	PK, PD, PP
Noncompliance with inclusion/exclusion criteria	2 (0.7)	3 (1.0)	5 (0.8)	PK, PD, PP
Changes in joint assessor where the data is questionable	0	0	0	PK, PD, PP
An assessment out of window by more than 2 weeks for Dose 6	2 (0.7)	3 (1.0)	5 (0.8)	PK, PD, PP
Receipt of corticosteroids[2]	4 (1.3)	5 (1.6)	9 (1.5)	PK, PD, PP
Patients who did not receive all doses of study treatment up to Week 30	48 (15.9)	44 (14.5)	92 (15.2)	PP
Patients who did not have an ACR assessment at Week 30	45 (14.9)	43 (14.1)	88 (14.5)	PP
Patients who discontinued or reduced their methotrexate dose for more than 2 consecutive weeks up to Week 30	2 (0.7)	1 (0.3)	3 (0.5)	PP

ACR, American College of Rheumatology; PD, pharmacodynamic; PK, pharmacokinetic; PP, per-protocol.

1. Indication of the analysis populations from which the protocol deviation excluded patients.
2. Except oral glucocorticoids, of maximum equivalent daily dose of 10 mg of prednisolone (patients were permitted to receive low potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations were administered per the instructions on the product label) and except for those corticosteroids administered due to progression of rheumatoid arthritis.

Baseline data

Demographic characteristics

Demographic characteristics were similar in the 2 treatment groups. The mean age in the study population was 49 years, with a majority of female (83%) and white (73%) patients. More than half the patients (54%) had a serum CRP level ≤ 2 mg/dL.

Table 26 Demographic characteristics (All-randomised population)

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=304)	Total (N=606)
Age (years)			
n	302	304	606
Mean (SD)	49.0 (12.18)	48.6 (11.49)	48.8 (11.83)
Median	50.0	50.0	50.0
Minimum, maximum	18, 75	21, 74	18, 75
Sex, no. (%)			
Male	57 (18.9)	48 (15.8)	105 (17.3)
Female	245 (81.1)	256 (84.2)	501 (82.7)
Race, no. (%)			
White	220 (72.8)	222 (73.0)	442 (72.9)
Black	2 (0.7)	1 (0.3)	3 (0.5)
Asian	34 (11.3)	37 (12.2)	71 (11.7)
Other	46 (15.2)	44 (14.5)	90 (14.9)
Height (cm)			
n	302	304	606
Mean (SD)	163.15 (8.739)	162.89 (9.021)	163.02 (8.875)
Median	162.30	162.00	162.00
Minimum, maximum	144.0, 186.0	124.0, 190.0	124.0, 190.0
Weight (kg)			
n	302	304	606
Mean (SD)	70.74 (16.322)	69.86 (15.760)	70.30 (16.036)
Median	69.00	68.00	68.55
Minimum, maximum	36.5, 134.0	36.0, 136.0	36.0, 136.0
Body mass index (kg/m^2)			
n	302	304	606
Mean (SD)	26.48 (5.271)	26.26 (5.273)	26.37 (5.269)
Median	26.28	25.40	25.85
Minimum, maximum	13.9, 49.8	15.0, 53.1	13.9, 53.1
Region, no. (%)			
European	179 (59.3)	180 (59.2)	359 (59.2)
Non-European	123 (40.7)	124 (40.8)	247 (40.8)
Baseline serum CRP concentration, no. (%)			
≤2 mg/dL	163 (54.0)	167 (54.9)	330 (54.5)
>2 mg/dL	139 (46.0)	137 (45.1)	276 (45.5)

CRP, C-reactive protein.
Note: The number of patients within each treatment group was used as the denominator for percentages.

Concomitant medications

For both the initial dose of MTX (taken at the date of first infusion) and the most recent dose of MTX, the mean (SD) dose taken was similar in the treatment arms. For the initial dose of MTX, the mean (SD) dose was 15.62 (3.10) mg/week and 15.61 (3.15) mg/week in the CT-P13 and Remicade treatment groups, respectively. For the most recent dose of MTX, the mean (SD) dose was 15.43 (2.94) mg/week and 15.52 (3.21) mg/week in the CT-P13 and Remicade treatment groups, respectively.

The most frequently reported concomitant medications were anti-inflammatory and antirheumatic products (199 [66.1%] patients and 199 [66.1%] patients in the CT-P13 and Remicade treatment groups, respectively), corticosteroids for systemic use (207 [68.8%] patients and 180 [59.8%] patients in the CT-P13 and Remicade treatment groups, respectively), and antihistamines for systemic use (140 [46.5%] patients and 142 [47.2%] patients in the CT-P13 and Remicade treatment groups, respectively).

Numbers analysed

The analysis populations are summarised below.

Table 27 Analysis populations

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=304)	Total (N=606)
	Number (%) of Patients		
Pharmacokinetic population	292 (96.7)	289 (95.1)	581 (95.9)
Pharmacokinetic (antibody negative subset) population	139 (46.0)	141 (46.4)	280 (46.2)
Pharmacodynamic population	292 (96.7)	290 (95.4)	582 (96.0)
Per-protocol population	248 (82.1)	251 (82.6)	499 (82.3)
All-randomized population	302 (100)	304 (100)	606 (100)
Safety population[1]	301 (99.7)	301 (99.0)	602 (99.3)
Other exclusions from the all-randomized population			
Patients from potentially fraudulent study centers	7	4	11

Note: The all-randomized population was used as the denominator for percentages.

1. Due to an incorrect kit being dispensed, 1 patient randomly assigned to the Remicade treatment group received 1 dose of CT-P13 at Week 2.

Outcomes and estimation

Primary endpoint

In the all-randomised population, the proportion of ACR20 responders at Week 30 was similar in the CT-P13 and Remicade treatment arms (184 [60.9%] patients and 178 [58.6%] patients, respectively). The 95% CI for the estimate of the treatment difference was entirely contained within the range -0.15 to + 0.15 (95% CI: -0.06, 0.10) indicating therapeutic equivalence between the treatment arms. The results for the PP population supported the results for the all-randomised population. The sensitivity analysis including patients from the potentially fraudulent study centre indicated a similar trend to the main analysis.

Table 28 Proportion of ACR20 responders at Week 30 (exact binomial method)

Treatment Group	n/N′ (%)	Estimate of Treatment Difference[1]	95% CI of Treatment Difference[2]
All-Randomized Population			
CT-P13	184/302 (60.9)	0.02	(–0.06, 0.10)
Remicade	178/304 (58.6)		
Per-Protocol Population			
CT-P13	182/248 (73.4)	0.04	(–0.04, 0.12)
Remicade	175/251 (69.7)		

ACR20, American College of Rheumatology definition of a 20% improvement; CI, confidence interval.
Note: N′=the number of patients with an assessment, n=the number of patients with the event, (%)=n/N′×100.

1. Estimate of the difference in proportions between the 2 treatment groups (CT-P13 – Remicade) using the exact binomial test.
2. Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

Other sensitivity analyses for the primary efficacy endpoint are summarised below. Their results supported those of the primary analysis.

Table 29 Proportion of ACR20 responders at Week 30 (logistic regression)

Treatment Group	n/N' (%)	Estimate[1]	Estimate of Treatment Difference[2]	95% CI of Treatment Difference[3]
All-randomised Population				
CT-P13	184/302 (60.9)	0.61	0.02	(-0.05, 0.10)
Remicade®	178/304 (58.6)	0.59		
Goodness-of-fit test (*P* value 0.990)[4]				
PP Population				
CT-P13	182/248 (73.4)	0.73	0.04	(-0.04, 0.12)
Remicade®	175/251 (69.7)	0.70		
Goodness-of-fit test (*P* value 0.915)[4]				

Note: N'=the number of subjects with an assessment, n=the number of subjects with the event, (%)=n/N'*100.
ACR20, 20% response, as defined by the American College of Rheumatology; CI, confidence interval.
[1] Estimates of proportions were calculated using a logistic regression model with treatment as a fixed effect and region and C-reactive protein category as covariates.
[2] The estimate of treatment difference of proportions (CT-P13 – Remicade®) and corresponding 95% CI were estimated from the logistic regression results using the Delta method. This method assumed independence between treatment groups.
[3] Therapeutic equivalence was concluded if the 95% CI of the treatment difference was entirely contained within the range -15% to 15%.
[4] P-value was calculated using the Hosmer-Lemeshow test for the goodness-of-fit of the logistic regression model. The test was significant at the 5% level.

Secondary endpoints

Individual components of the ACR criteria

In both the all-randomised and PP populations, mean decreases from baseline to Week 14 and 30 were similar in the CT-P13 and Remicade treatment groups for the ACR components.

Table 30 Summary of changes in ACR components (All-randomised population)

ACR component	CT-P13 (N=302) (Mean±SD)	Remicade (N=304) (Mean±SD)
Number of Tender Joints		
Baseline	25.6 ± 13.87	24.0 ± 12.94
Week 14	-14.1 ± 11.69	-14.1 ± 11.64
Week 30	-16.2 ± 11.75	-15.6 ± 12.86
Number of Swollen Joints		
Baseline	16.2 ± 8.68	15.2 ± 8.27
Week 14	-10.6 ± 8.42	-10.0 ± 8.02
Week 30	-12.2 ± 8.87	-11.5 ± 9.07
Patient assessment of pain (VAS, 0-100)		
Baseline	65.9 ± 17.44	65.5 ± 17.22
Week 14	-28.4 ± 23.88	-27.1 ± 23.52
Week 30	-29.3 ± 25.69	-27.7 ± 25.18
Patient global assessment of disease activity (VAS 0-100)		
Baseline	65.7 ± 17.21	65.4 ± 17.00
Week 14	-28.8 ± 23.23	-25.7 ± 24.70
Week 30	-27.7 ± 26.25	-26.9 ± 26.07
Physician global assessment of disease activity (VAS 0-100)		
Baseline	64.7 ± 14.31	65.0 ± 13.52
Week 14	-34.4 ± 20.97	-33.2 ± 20.42
Week 30	-35.7 ± 20.63	-35.1 ± 21.18

ACR component	CT-P13 (N=302) (Mean±SD)	Remicade (N=304) (Mean±SD)
HAQ Physical Ability (scale 0-3)		
Baseline	1.61 ± 0.55	1.56 ± 0.59
Week 14	-0.56 ± 0.56	-0.50 ± 0.52
Week 30	-0.60 ± 0.59	-0.51 ± 0.57
CRP (mg/dL)		
Baseline	1.90 ± 2.51	1.89 ± 2.19
Week 14	-0.60 ± 2.94	-0.80 ± 1.93
Week 30	-0.69 ± 2.33	-0.74 ± 1.95
ESR (mm/h)		
Baseline	46.5 ± 22.30	48.5 ± 22.60
Week 14	-13.7 ± 20.85	-16.9 ± 19.51
Week 30	-15.3 ± 20.81	-15.7 ± 21.79

ACR response

The proportion of ACR responders at Week 14 and 30 is shown in the below table. For each of the parameters, there was no evidence of a statistically significant difference between the CT-P13 and Remicade treatment groups at the 5% level of significance. However, all point estimates showed a higher response rate for CT-P13 than Remicade, especially at Week 14 where the 95% CI upper limit was close to +0.15 for ACR20 and ACR50.

Table 31 Proportion of ACR responders at Weeks 14 and 30 (exact binominal method) (PP population)

Visit	Efficacy Parameter	Treatment Arm	n/N' (%)	Estimate of Treatment Difference	95% CI of Treatment Difference
Week 14	ACR20	CT-P13	180/248 (72.6)		
		Remicade	164/251 (65.3)	0.07	(-0.01, 0.15)
	ACR50	CT-P13	98/248 (39.5)		
		Remicade	85/251 (33.9)	0.06	(-0.03, 0.14)
	ACR70	CT-P13	41/248 (16.5)		
		Remicade	34/251 (13.5)	0.03	(-0.03, 0.09)
Week 30	ACR50	CT-P13	105/248 (42.3)		
		Remicade	102/251 (40.6)	0.02	(-0.07, 0.10)
	ACR70	CT-P13	50/248 (20.2)		
		Remicade	45/251 (17.9)	0.02	(-0.05, 0.09)

Additional analyses conducted at Week 54 further supported comparable efficacy of CT-P13 and Remicade.

Table 32 Proportion of ACR responders at Week 54 (exact binomial method) (PP Population)

ACR Scores	n/N (%)		Estimate of Treatment Difference	95% CI of Treatment Difference
	CT-P13	Remicade		
ACR20	168/246 (68.3)	155/250 (62.0)	0.06	-0.02, 0.15
ACR50	98/246 (39.8)	94/250 (37.6)	0.02	-0.06, 0.11
ACR70	48/246 (19.5)	44/250 (17.6)	0.02	-0.05, 0.09

Disease activity measured by DAS28

The mean scores for disease activity and number of tender joints and swollen joints measured by DAS28 decreased from baseline at Weeks 14 and 30 in both treatment arms. The analysis of DAS28 at Weeks 14 and 30 is summarised for the PP population in the table below. The 95% CIs for the estimate of treatment difference contained 0, hence there was no evidence of a difference between the CT-P13 and Remicade treatment arms in change from baseline in DAS28 (ESR) or DAS28 (CRP) at either time point at the 5% level of significance.

Table 33 DAS28 ANCOVA (PP population)

Visit / Treatment Arm	N	Adjusted Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
DAS28 (ESR)				
Week 14				
CT-P13	246	4.42 (0.074)	-0.11	(-0.31, 0.09)
Remicade	249	4.53 (0.074)		
Week 30				
CT-P13	245	4.21 (0.084)	-0.10	(-0.33, 0.13)
Remicade	249	4.31 (0.083)		
DAS28 (CRP)				
Week 14				
CT-P13	246	3.71 (0.072)	-0.15	(-0.35, 0.05)
Remicade	249	3.86 (0.071)		
Week 30				
CT-P13	246	3.61 (0.080)	-0.05	(-0.27, 0.16)
Remicade	249	3.66 (0.080)		

CI=confidence interval; CRP=C-reactive protein; DAS28=Disease Activity Score 28; ESR=erythrocyte sedimentation rate; SE=standard error.

Other endpoints

The mean decreases from baseline in SDAI and CDAI and the proportions of patients with a good response according to EULAR criteria were similar at both time points in the CT-P13 and Remicade treatment arms. Likewise, mean increases from baseline at Weeks 14 and 30 were similar in both treatment arms for SF-36 components, including fatigue.

Ancillary analyses

Analyses for multiplicity were not needed in this trial with only one primary efficacy endpoint. Consistency of ACR20 response rates was shown across geographic regions. No post-hoc analyses were performed for efficacy.

Summary of main study

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

Table 34 Summary of efficacy for study CT-P13 3.1

Title: A randomised, double-blind, parallel-group, phase III study to demonstrate equivalence in efficacy and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis			
Study identifier	CT-P13 3.1		
Design	Double-blind, randomised, multicentre in 100 centres (19 countries)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		30 weeks (6 infusions) not applicable 24 weeks (total 9 infusions)
Hypothesis	Equivalence		
Treatments groups	CT-P13		3mg/kg IV at Week 0, 2, 6, 14, 22, 30 combined with methotrexate number randomised: 302
	Remicade		3mg/kg IV at Week 0, 2, 6, 14, 22, 30 combined with methotrexate number randomised: 304
Endpoints and definitions	Primary endpoint	ACR20 W30	% patients achieving ACR20 response at week 30
	Secondary endpoint	ACR20 W14	% patients achieving ACR20 response at week 14
	Secondary endpoint	ACR50 W14	% patients achieving ACR50 response at week 14
	Secondary endpoint	ACR50 W30	% patients achieving ACR50 response at week 30
	Secondary endpoint	DAS28 (ESR) W14	DAS28 (ESR) change from BL at Week 14
	Secondary endpoint	DAS28 (ESR) W30	DAS28 (ESR) change from BL at Week 30
	Secondary endpoint	SF36 PF W14	SF36 Physical function change from BL at Week 14
	Secondary endpoint	SF36 PF W30	SF36 Physical function change from BL at Week 30
Database lock	Data cut-off: 20 December 2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol & All-randomised At Week 30		
Descriptive statistics and estimate variability	Treatment group	CT-P13	Remicade
	Number of subjects	302	304
	ACR20 W30 (%) ALL-R PP	184/302 (60.9) 182/248 (73.4)	178/304 (58.6) 175/251 (69.7)
	ACR20 W14 (%) PP	180/248 (72.6)	164/251 (65.3)
	ACR50 W14 (%) PP	98/248 (39.5)	85/251 (33.9)
	ACR50 W30 (%) PP	105/248 (42.3)	102/251 (40.6)
	DAS28 (ESR) W14 Mean (SD) change PP	-2.22 ± 1.22	-2.10 ± 1.11
	DAS28 (ESR) W30 Mean (SD) change PP	-2.44 ± 1.39	-2.31 ± 1.27
	SF36 PF W14 Mean (SD) change PP	7.49 ± 9.42	5.90 ± 8.22

	SF36 PF W30 Mean (SD) change PP	7.63 ± 10.59	6.84 ± 9.00
Effect estimate per comparison	Primary endpoint **ACR20 W30** ALL-R	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	0.02
		95%CI	-0.06; 0.10
		Test	-15% < CI < +15%
	Primary endpoint **ACR20 W30** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	0.04
		95% CI	-0.04; 0.12
		Test	-15% < CI < +15%
	Secondary endpoint **ACR20 W14** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	0.07
		95% CI	-0.01; 0.15
		Test	-15% < CI < +15%
	Secondary endpoint **ACR50 W14** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	0.06
		95% CI	-0.03; 0.14
		Test	-15% < CI < +15%
	Secondary endpoint **ACR50 W30** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	0.02
		95% CI	-0.07; 0.10
		Test	-15% < CI < +15%
	Secondary endpoint **DAS28 W14** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	-0.11
		95% CI	-0.31; 0.09
	Secondary endpoint **DAS28 W30** PP	Comparison groups	CT-P13 vs. Remicade
		Treatment difference	-0.10
		95% CI	-0.33; 0.13

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

No meta- or pooled analyses were performed for efficacy.

Clinical studies in special populations

No clinical studies in special population were performed.

2.5.3. Supportive study

Study CT-P13 1.1: a randomised, double-blind, parallel-group, phase I study to demonstrate the equivalence with respect to the pharmacokinetic profile of CT-P13 and Remicade in patients with ankylosing spondylitis.

This section focuses on the efficacy parameters and results.

Methods

Study participants

Main inclusion criteria:

- Male or female aged 18 to 75 years old;
- Diagnosis of active AS according to the 1984 modified New York classification criteria [van der Linden et al 1984] for at least 3 months prior to Screening;
- Active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (range 0 to 10) at Screening in spite of following conventional treatment for AS for at least 3 months prior to Screening;
- Visual analogue scale score for spinal pain of ≥4 (range 0 to 10).

Main exclusion criteria:

- Tuberculosis (TB), other severe or chronic infections, bone marrow hypoplasia;
- Diabetes mellitus, unless on a stable dosing regimen for at least 4 weeks prior to screening;
- Any other inflammatory or rheumatic diseases;
- History of any malignancy (within the previous 5 years except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma), lymphoma or lymphoproliferative disease;
- History of congestive heart failure (New York Heart Association class III/IV) or unstable angina.

Prohibited concomitant medications

- Corticosteroids, except oral glucocorticoids of maximum equivalent daily dose of 10 mg of prednisolone within 4 weeks prior to screening;
- DMARDs including hydroxychloroquine, chloroquine, MTX, or sulfasalazine, within 4 weeks prior to screening;
- Alkylating agents within 12 months prior to screening;
- Live or live-attenuated vaccine within 8 weeks of screening;
- Any biological agents for the treatment of AS.

Treatment

Patients received a 2-hour IV infusion of either CT-P13 (5 mg/kg) or Remicade (5 mg/kg) at Weeks 0, 2, and 6 and then once every 8 weeks up to Week 54. This corresponds to 3 loading doses and 6 maintenance doses.

Objectives

The primary objective of this study was to demonstrate comparable PK at steady state between CT-P13 and Remicade in patients with AS up to Week 30. The secondary objectives of this study were to assess the long-term efficacy, PK and overall safety of CT-P13 in comparison with Remicade up to Week 54.

Efficacy endpoints

The efficacy was assessed at Week 14 and 30 by the following parameters:

- Proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria

- BASDAI, BASFI, BASMI compared with baseline
- Chest expansion compared with baseline
- QoL questionnaire (Medical Outcomes Study Short term Health Survey [SF 36])

The ASAS20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI
- Morning stiffness determined using the last 2 questions of BASDAI

Additionally, ASAS20 responders should not have deterioration (worsening of ≥20% and an absolute worsening of at least 1 unit on a 0 to 10 scale) of the remaining assessment domain compared to baseline. ASAS40 responder are defined as an improvement of at least 40% and an absolute improvement of at least 2 units on a 0 to 10 scale from baseline in at least 3 of the 4 domains of the ASAS20, with no deterioration from baseline in the remaining domain. For the analyses of ASAS20 and ASAS40 at Weeks 14 and 30, patients who had an assessment and had recorded missing values at that visit for any of the 4 components of ASAS20/ASAS40 were classified as non-responders.

Sample size

A total of 246 male or female patients were to be enrolled in the study. Assuming a CV of 50%, an expected ratio of means equal to 1, a 2-sided alpha equal to 0.1, a power equal to 90%, and a 2-sided equivalence margin of 80% to 125% for AUC_T and $C_{max,ss}$, a recruitment of 196 patients was required. Allowing for a dropout rate of 20% would mean that 246 patients would need to be randomly assigned to treatment in total. In total 250 patients were enrolled in the study (all-randomised population).

Randomisation

Randomisation of patients was conducted using an interactive voice response system (IVRS). It was stratified by region and baseline BASDAI score.

Blinding (masking)

This study was patient, investigator and sponsor-blinded. At Week 30, the study was unblinded for reporting purposes; the study remained blinded to the investigators and patients up to Week 54.

Statistical methods (efficacy analysis)

The efficacy parameters were assessed on the all-randomised population, which consisted of all patients enrolled and randomly assigned to receive a dose of either of the study treatments, regardless of whether or not any study treatment dosing was completed.

For ASAS20 and ASAS40, the proportion of overall responders was analysed by a logistic regression model, with randomised treatment arm as a fixed effect and the stratification factors (region, baseline BASDAI score) as covariates. Treatment effects were estimated by calculating the odds ratio and 95% CI. For the other parameters, descriptive statistics for actual values and change from baseline were calculated by treatment and study visit.

Efficacy Results

Participant flow and baseline characteristics

These are described in section 2.3.2 up to Week 30.

The week 54 results update showed that 210 patients completed the study (106/125 [84.8%] in the CT-P13 group and 104/125 [83.2%] in the Remicade group). By Week 54, 40/250 (16%) patients had discontinued, 19/125 (15.2%) in the CT-P13 group and 21/125 (16.8%) in the Remicade group. The primary reasons for discontinuation were adverse events (10/125 [8.0%] and 8/125 [6.4%] patients in the CT-P13 and Remicade group, respectively), and withdrawal of consent by the patient (3/125 [2.4%] and 6/125 [4.8%] patients in the CT-P13 and Remicade group, respectively).

Demographic and baseline characteristics were similar in the 2 treatment groups. In total, there were a greater percentage of male patients compared with female patients, i.e. 99/125 (79.2%) in the CT-P13 group and 103/125 (82.4) in the Remicade group. Mean age was 39.2 years in the CT-P13 group and 38.7 years in the Remicade group. The majority of patients were White (75.6%) and from European region (64.8%). The majority of patients (187 [74.8%]) had a baseline BASDAI score of <8 (92 [73.6%] patients and 95 [76.0%] patients in the CT-P13 and Remicade treatment groups, respectively). The BASDAI score at baseline was ≥8 in 33/125 (26.4%) and in 30/125 (24.0%) in the CT-P13 and Remicade group, respectively.

Outcomes and estimation

ASAS20 and ASAS40 responses

The proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Weeks 14 and 30 was similar in the CT-P13 and Remicade treatment arms. The 95% CI contained 1 for both criteria at each of the time points and hence there was no evidence of a difference between CT-P13 and Remicade at either visit at the 5% level of significance.

Table 35 ASAS20 and ASAS40 responses (All-randomised population)

Visit	Efficacy Parameter	Treatment Arm	Responders n/N (%)	Odds Ratio	95% CI of the Odds Ratio
Week 14	ASAS20	CT-P13	72/115 (62.6)	0.91	0.53, 1.54
		Remicade	79/122 (64.8)		
		Goodness-of-fit test (*p* value 0.819)			
	ASAS40	CT-P13	48/115 (41.7)	0.85	0.51, 1.42
		Remicade	56/122 (45.9)		
		Goodness-of-fit test (*p* value 0.875)			
Week 30	ASAS20	CT-P13	79/112 (70.5)	0.91	0.51, 1.62
		Remicade	84/116 (72.4)		
		Goodness-of-fit test (*p* value 0.854)			
	ASAS40	CT-P13	58/112 (51.8)	1.19	0.70, 2.00
		Remicade	55/116 (47.4)		
		Goodness-of-fit test (*p* value 0. 893)			

Results at Week 54 remained comparable with ASAS20 rates of 67.0% (71/106) in the CT-P13 arm and 69.4% (75/108) in the Remicade arm.

BASDAI, BASFI, BASMI, and Chest Expansion

Mean BASDAI, BASFI and BASMI scores decreased from baseline to Weeks 14 and 30 in both treatment arms. For all 3 scores, the mean decrease from baseline to both time points was similar in the CT-P13 and Remicade treatment arms. The mean chest expansion result increased from baseline to Weeks 14 and 30 in both treatment arms. The mean increase from baseline at both time points was similar in the CT-P13 and Remicade treatment arms.

Table 36 Summary of changes from baseline (All-randomised population)

Efficacy Parameter	CT-P13 (N=125)	Remicade (N=125)
BASDAI score		
Baseline, mean±SD (range)	6.74 ±1.41 (3.4-10.0)	6.57 ± 1.64 (1.8-10.0)
Mean change from baseline±SD (range)		
Week 14	-2.91 ± 2.17 (-9.0, 1.5)	-2.77 ± 2.08 (-10.0, 3.2)
Week 30	-3.04 ± 2.23 (-8.4, 2.6)	-2.71 ± 2.24 (-9.8, 6.2)
BASFI score		
Baseline, mean±SD (range)	6.20 ± 1.93 (0.7, 9.8)	6.24 ± 2.21 (0.1, 10.0)
Mean change from baseline±SD (range)		
Week 14	-2.51 ± 2.14 (-7.7, 2.8)	-2.47 ± 2.18 (-10.0, 2.8)
Week 30	-2.60 ± 2.19 (-7.5, 2.8)	-2.54 ± 2.17(-10.0, 3.8)
BASMI score		
Baseline, mean±SD (range)	4.0 ± 2.1 (0, 9)	4.1 ±2.1 (0, 9)
Mean change from baseline±SD (range)		
Week 14	-0.7 ± 1.2 (-4, 2)	-0.7 ± 1.4 (-6, 3)
Week 30	-1.0 ± 1.4 (-4, 2)	-0.9 ±1.4 (-6, 2)
Chest expansion (cm)		
Baseline, mean±SD (range)	3.16 ± 1.33 (0.5, 9.0)	2.87 ± 1.25 (0.0, 7.0)
Mean change from baseline±SD (range)		
Week 14	0.38 ± 1.04 (-3.5, 4.0)	0.66 ± 1.04 (-1.5, 6.0)
Week 30	0.56 ± 1.38 (-7.0, 3.5)	0.80 ± 1.18 (-1.5, 4.5)

Quality of Life Questionnaire (SF-36)

The mean SF-36 scores increased from baseline to Weeks 14 and 30 in both treatment arms. For each of the components, the mean change was similar in the CT-P13 and Remicade treatment arms.

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

Main study

Study CT-P13 3.1 is a randomised, double-blind, parallel-group study designed to demonstrate equivalence in efficacy and safety between CT-P13 and Remicade when co-administered with MTX in patients with active rheumatoid arthritis. Randomisation was stratified by geographic region and baseline CRP level (> 2.0 vs. ≤ 2.0 mg/dL).

A single pivotal equivalence trial comparing the test and reference products is considered adequate to support this biosimilar application. The trial was designed to show equivalence of the test and reference products if the 95% CI for the difference between treatments was entirely within -15% to +15% in both the all-randomised and PP populations. The choice of the indication (RA), the clinical setting (patients not adequately controlled with MTX), the primary endpoint (ACR20 at Week 30) and the equivalence margin (± 15%) are in line with the CHMP guidance and were endorsed in CHMP scientific advice. Indeed, this clinical model was considered sufficiently sensitive to enable the detection of differences between the two

products. The choice of the patient population was based on the effect size (infliximab vs. placebo) observed in the pivotal Remicade trials, which appeared larger in the ATTRACT trial (patients with inadequate response to MTX) than in the ASPIRE trial (with MTX in the first line).

The main secondary efficacy endpoints were the individual components of the ACR criteria, ACR20 at Week 14 as well as ACR50 and ACR70 at Weeks 14 and 30, decrease in disease activity measured by DAS28 (using both ESR and CRP), EULAR response, SDAI, CDAI, and SF-36 at Weeks 14 and 30.

The study was unblinded at Week 30 for reporting. However, the study was kept blinded to the investigators and patients until its end. The Applicant included the results of the primary analysis in the initial submission and provided the follow-up data up to 1 year (data collected up to Week 62) upon CHMP request.

CT-P13 and Remicade were administered as a dose of 3 mg/kg in a 2-hour IV infusion according to the approved posology of Remicade. Methotrexate (12.5 - 25 mg/week) was co-administered either via oral or parenteral route. The dose and the route were maintained from beginning to end of study. Folic acid (≥5 mg/week) was included in the co-medication in order to reduce the adverse effects of MTX.

Supporting study

The PK study CT-P13 1.1 was a randomised, double-blind, parallel-group comparison of CT-P13 and Remicade in patients with active AS with a BASDAI score ≥4 in spite of conventional treatment. Randomisation was stratified by region and baseline BASDAI score. The study was designed primarily to demonstrate the PK equivalence between CT-P13 and Remicade and efficacy was studied as part of the secondary objectives. The main efficacy criteria were the proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Weeks 14 and 30, as well as BASDAI, BASFI, BASMI, and SF-36 scores at Weeks 14 and 30 compared with baseline.

Both trials, CT-P13 1.1 and CT-P13 3.1, were conducted mainly in Eastern Europe and Latin America, with additional enrolment in Korea or Philippines, but few patients from Western-Europe. As similar results were shown across geographic regions, the CHMP considered it is acceptable.

Efficacy data and additional analyses

Study CT-P13 3.1

Patient demographics and disease characteristics were well balanced across the treatment arms, although there were slightly more women and white people with slightly higher disease activity in the CT-P13 arm. Overall, more than half the patients had a baseline CRP concentration ≤ 2 mg/dL. The results are robust as only 15-16% of patients discontinued before Week 30, mostly because of an adverse event or withdrawal of consent; no notable imbalance was observed between the treatment arms with regard to the reasons for discontinuation except for lack of efficacy (6 patients in the CT-P13 arm vs. none in the Remicade arm). However, in the updated analysis at Week 54, these figures became 10 vs. 6 patients, respectively.

The populations for the efficacy analysis included all randomised patients and the PP population, the main protocol violation being the omission of a scheduled infliximab infusion and the lack of ACR assessment. The concomitant treatments for RA were comparable, except for the use of systemic corticosteroids that was slightly more common in the CT-P13 arm (69%) than in the Remicade arm (60%); the mean dose of corticosteroid remained stable throughout the study in both treatment arms.

At Week 30, a similar proportion of patients in the CT-P13 (184/302, 60.9%) and the Remicade arm (178/304, 58.6%) achieved a clinical response according to ACR20 criteria in the all-randomised

population. The 95% CI for the estimated treatment difference (CT-P13 – Remicade = +2% [-6%, +10%]) was entirely contained within the range ±15% indicating therapeutic equivalence between the treatment groups. Similar results were reported in the PP population analysis. A sensitivity analysis using a logistic regression model produced almost identical CIs in both the all-randomised and PP populations; so the conclusion is robust to the method of analysis. The CIs did not change if the patients from the potentially fraudulent centre (11 in total) were included in the analysis. Consistency of ACR20 response rates was shown across geographic regions with expected random fluctuation of the difference between the test and reference products. It was noted that the response rate was higher in this trial (60-70%) compared with the ATTRACT trial, the pivotal trial for Remicade, and the Applicant's assumption (50%). It was also noted that baseline CRP levels were lower than in the ATTRACT trial, leading to the possibility that a population with less severe disease had been enrolled. The Applicant further justified the assay sensitivity of the trial based on a discussion of all published studies available with Remicade; moreover, the data from study CT-P13 3.1 did not suggest a correlation between baseline CRP level and response rate.

Overall, based on these data, equivalence of the ACR20 response at Week 30 was demonstrated in both all-randomised and PP populations. The point estimates were numerically in favour of CT-P13 and non-inferiority was clearly demonstrated as the CI lower bounds were well above -10%, which is a preferred margin from a clinical perspective. Therefore, this result provides clear assurance that CT-P13 is not inferior to Remicade. At week 30, the results of the secondary endpoints (in particular ACR50 and ACR70, decreases in DAS28, SDAI and CDAI, increases in SF-36) were all consistent with the results of the primary endpoint with estimates of treatment effect numerically in favour of CT-P13. At the earlier time point of Week 14, which may be more sensitive to detect potential differences before the response rate reaches its plateau, the point estimates for ACR20 response were also numerically greater with CT-P13 than with Remicade in both the PP and all-randomised populations; although the treatment difference reached +7% (PP analysis), the 95% upper limit of the CI was 15%, the predefined acceptance margin to demonstrate equivalence. The decrease in disease activity measured by DAS28 appeared in line with the ACR response results with estimates of treatment differences in favour of CT-P13, especially at Week 14. All 95% CIs were well contained within the interval of ± 0.6, which corresponds to the maximum change in DAS score considered as "no response" according to EULAR criteria. Likewise, estimates of the other secondary endpoints generally showed numerical trends in favour of CT-P13, especially at Week 14.

During the procedure the Applicant provided Week 54 efficacy results in the PP population. The proportion of patients achieving clinical response according to the ACR20, ACR50, and ACR70 criteria at Week 54 remained numerically in favour of CT-P13 compared with Remicade, with 95% CIs for the treatment differences contained within ±15%. Comparable results were also observed for the secondary endpoints. Therefore, these results further support a comparable efficacy of CT-P13 and Remicade.

Study CT-P13 1.1

Overall, treatment arms were comparable for demographic characteristics and baseline disease activity index. The proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Weeks 14 and 30 was similar in the CT-P13 and Remicade treatment arms in the all-randomised population. No evidence of difference was observed between CT-P13 and Remicade at the 5% level of significance. Mean BASDAI, BASFI and BASMI score decreased similarly from baseline to Weeks 14 and 30 in both treatment arms. During the procedure the Applicant provided Week 54 efficacy results, which showed comparable ASAS20 responder rates. In contrast to the pivotal RA trial, no trend was observed in favour of either product in this AS population.

Overall, although this supportive efficacy study in AS patients was not powered to show therapeutic equivalence, the results were comparable between treatment arms, as reflected by ASAS20 and ASAS40 responses and decreases in BASDAI and BASFI.

2.5.5. Conclusions on the clinical efficacy

The pivotal efficacy study CT-P13 3.1 conducted in RA patients provided robust evidence of therapeutic equivalence based on ACR20 response at Week 30, the primary endpoint, as well as all secondary efficacy parameters. While the results were numerically in favour of CT-P13, the 95% CIs of the treatment differences remained confined within the predefined therapeutic equivalence margin of ±15%. These data were further supported by comparable response rates at 1 year.

Additional supportive efficacy data were provided in another indication by the PK study CT-P13 1.1 conducted in AS patients. The efficacy results were comparable between treatment arms up to Week 54, with no trend favouring either product.

2.6. Clinical safety

The safety data of CT-P13 were collected in the 3 clinical trials: the pilot trial CT-P13 1.2 in RA patients, the pivotal PK trial in AS patients CT-P13 1.1, and the pivotal efficacy trial CT-P13 3.1 in RA patients. The safety analysis was performed on the safety population defined as all patients who received at least one full or partial dose of either of the study treatments during any dosing period. The safety monitoring included monitoring of adverse events (AEs), serious adverse event (SAE), treatment-emergent adverse events (TEAEs), serious TEAEs, death, hypersensitivity via vital signs, electrocardiogram (ECG), physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis (TB), and pregnancy. Infections, infusion-related reactions and safety issues of special interest for infliximab were closely monitored. The areas of special interest were heart failure, serious infections (including TB, Hepatitis B virus reactivation, sepsis and opportunistic infections) as well as serious infusion reactions, delayed hypersensitivity reactions (serum sickness), systemic lupus erythematosus/lupus-like syndrome, hepatobiliary events, demyelinating disorders (i.e. multiple sclerosis, Guillain-Barré syndrome), haematologic reactions, lymphoma (including hepatosplenic T-cell lymphoma).

Patient exposure

In total, 871 patients were included in the safety population of all 3 studies:

- Study CT-P13 3.1: 602 RA patients (301 patients in each treatment group)
- Study CT-P13 1.1: 250 AS patients (128 patients treated with CT-P13 and 122 with Remicade)
- Study CT-P13 1.2: 19 RA patients (10 patients treated with CT-P13 and 9 with Remicade)

In the initial submission, the data cut-off corresponded to a minimum exposure of 30 weeks for all ongoing patients. There were 263 patients with RA and 117 patients with AS exposed to CT-P13 for at least 30 weeks of treatment.

In Study CT-P13 3.1, the total number of doses received by Week 30 was similar in the CT-P13 and Remicade arms (mean of 5.6 doses). The mean total dose administered was 1191.6±357.361 mg in the CT-P13 arm and 1178.3±347.778 mg in the Remicade arm, respectively.

Table 37 Overall exposure up to Week 30 in Study CT-P13 3.1 (Safety population)

Study week	CT-P13	Remicade
Week 0	301	301

Week 14	276 (91.7%)	277 (92.0%)
Week 22	269 (89.4%)	266 (88.4%)
Week 30	256 (85.0%)	259 (86.0%)

In the safety update up to Week 54, the mean total number of doses was 8.0 in the CT-P13 arm and 7.9 in the Remicade arm (maximum 9). The mean total dose administered was 1712±608 mg in the CT-P13 arm and 1673±595 mg in the Remicade arm, respectively.

In Study CT-P13 1.1, the mean total number of doses received by Week 54 was 8.4 doses and 8.5 doses in the CT-P13 and Remicade arms, respectively. The mean total dose administered by Week 54 was 3187±969 mg and 3258±862 mg in the CT-P13 and Remicade arms, respectively.

Adverse events

- **Study CT-P13 3.1**

In the initial safety analysis, the number (percentage) of patients reporting TEAEs was 181 (60%) in the CT-P13 arm compared to 183 (61%) in the Remicade arm. The total number of TEAEs was 487 in the CT-P13 vs. 490 in the Remicade arm.

Table 38 Summary of TEAEs in Study CT-P13 3.1 (Safety population)

	CT-P13 3.1		
	CT-P13	**Remicade**	**Total**
N (%) of pat with at least 1 TEAE	181 (60.1)	183 (60.8)	364 (60.5)
TEAEs	487	490	977
N (%) of pat with drug related TEAEs	106 (35.2)	108 (35.9)	214 (35.5)
N (%) of pat with at least 1 treatment emergent SAEs	30 (10.0)	21 (7.0)	51 (8.5)
Treatment-emergent SAEs	35	22	57
N (%) of pat with treatment emergent, drug related SAEs	17 (5.6)	10 (3.3)	27 (4.5)
N (%) of discontinued pat due to at least 1 TEAE	29 (9.6)	26 (8.6)	55 (9.1)
TEAEs leading to discontinuation	35	30	65
N (%) of discontinued pat due to drug related TEAE	27 (9.0)	20 (6.6)	47 (7.8)
Deaths	0	0	0
N (%) of pat with drug-related infections	46 (15.3)	51 (16.9)	97 (16.1)
N (%) of pat with infusion-related reactions	3 (1.0)	6 (2.0)	9 (1.5)

The most frequently reported TEAEs (in ≥5% patients in any treatment arm) included: latent tuberculosis (6.3% vs. 6.0% patients, respectively), nasopharyngitis (6.3% vs. 5.0%), hypertension (5.3% vs. 2.7%), increased ALT (4.0% vs. 5.3%) and headache (3.0% vs. 5.3%). All TEAEs reported in ≥1% of patients in any treatment arm are summarised below.

Table 39 Most common TEAEs in RA patients (≥1% of patients in any treatment arm)

System Organ Class **Preferred Term** **(MedDRA)**	**Study CT-P13 3.1**	
	CT-P13 3 mg/kg	**Remicade 3 mg/kg**
	N=301	**N=301**
Number of events (TEAEs)	487	490
Number of patients with any event (TEAE)	181 (60.1)	183 (60.8)
Drug-related	*106 (35.2)*	*108 (35.9)*
Blood and lymphatic system disorders	**14 (4.7)**	**14 (4.7)**
Anaemia	6 (2.0)	8 (2.7)
Leukopenia	1 (0.3)	5 (1.7)
Neutropenia	3 (1.0)	2 (0.7)

System Organ Class Preferred Term (MedDRA)	Study CT-P13 3.1	
	CT-P13 3 mg/kg	Remicade 3 mg/kg
	N=301	N=301
Cardiac disorders	**5 (1.7)**	**6 (2.0)**
Bradycardia	0	3 (1.0)
Ear and labyrinth disorders	**5 (1.7)**	**0**
Vertigo	3 (1.0)	0
Eye disorders	**12 (4.0)**	**3 (1.0)**
Cataract	3 (1.0)	1 (0.3)
Gastrointestinal disorders	**19 (6.3)**	**25 (8.3)**
Abdominal pain	3 (1.0)	1 (0.3)
Abdominal pain upper	2 (0.7)	3 (1.0)
Diarrhoea	3 (1.0)	6 (2.0)
Gastritis	1 (0.3)	4 (1.3)
Nausea	1 (0.3)	5 (1.7)
Vomiting	0	3 (1.0)
General disorders and administration site conditions	**14 (4.7)**	**18 (6.0)**
Asthenia	4 (1.3)	1 (0.3)
Infusion-related reaction	3 (1.0)	6 (2.0)
Pyrexia	0	7 (2.3)
Immune system disorders	**11 (3.7)**	**11 (3.7)**
Drug hypersensitivity	5 (1.7)	9 (3.0)
Hypersensitivity	3 (1.0)	2 (0.7)
Infections and infestations	**95 (31.6)**	**107 (35.5)**
Bronchitis	8 (2.7)	12 (4.0)
Gastroenteritis	5 (1.7)	7 (2.3)
Herpes zoster	2 (0.7)	4 (1.3)
Influenza	6 (2.0)	2 (0.7)
Latent tuberculosis	19 (6.3)	18 (6.0)
Nasopharyngitis	19 (6.3)	15 (5.0)
Pharyngitis	5 (1.7)	7 (2.3)
Oral herpes	1 (0.3)	5 (1.7)
Rhinitis	3 (1.0)	6 (2.0)
Tooth abscess	0	4 (1.3)
Upper respiratory tract infection	12 (4.0)	9 (3.0)
Urinary tract infection	13 (4.3)	12 (4.0)
Injury, poisoning and procedural complications	**10 (3.3)**	**5 (1.7)**
Contusion	4 (1.3)	1 (0.3)
Investigations	**36 (12.0)**	**39 (13.0)**
Alanine aminotransferase increased	12 (4.0)	16 (5.3)
Aspartate aminotransferase increased	6 (2.0)	9 (3.0)
Blood creatine phosphokinase increased	3 (1.0)	6 (2.0)
Blood pressure increased	2 (0.7)	3 (1.0)
Gamma-glutamyltransferase increased	3 (1.0)	4 (1.3)
Hepatic enzyme increased	6 (2.0)	1 (0.3)
Transaminases increased	3 (1.0)	2 (0.7)
Metabolism and nutrition disorders	**6 (2.0)**	**3 (1.0)**
Hypokalaemia	3 (1.0)	2 (0.7)
Musculoskeletal and connective tissue disorders	**33 (11.0)**	**22 (7.3)**
Arthralgia	3 (1.0)	1 (0.3)
Back pain	3 (1.0)	4 (1.3)
Bone pain	3 (1.0)	2 (0.7)
Muscle spasms	1 (0.3)	3 (1.0)
Osteoarthritis	3 (1.0)	1 (0.3)
Rheumatoid arthritis	13 (4.3)	7 (2.3)

System Organ Class Preferred Term (MedDRA)	Study CT-P13 3.1	
	CT-P13 3 mg/kg	Remicade 3 mg/kg
	N=301	N=301
Nervous system disorders	**18 (6.0)**	**29 (9.6)**
Dizziness	2 (0.7)	3 (1.0)
Headache	9 (3.0)	16 (5.3)
Psychiatric disorders	**6 (2.0)**	**4 (1.3)**
Anxiety	2 (0.7)	3 (1.0)
Renal and urinary disorders	**9 (3.0)**	**8 (2.7)**
Haematuria	2 (0.7)	3 (1.0)
Reproductive system and breast disorders	**6 (2.0)**	**8 (2.7)**
Metrorrhagia	0	3 (1.0)
Respiratory, thoracic and mediastinal disorders	**13 (4.3)**	**10 (3.3)**
Cough	5 (1.7)	2 (0.7)
Oropharyngeal pain	3 (1.0)	4 (1.3)
Skin and subcutaneous tissue disorders	**18 (6.0)**	**21 (7.0)**
Rash	2 (0.7)	5 (1.7)
Vascular disorders	**24 (8.0)**	**13 (4.3)**
Hypertension	16 (5.3)	8 (2.7)

The proportion of patients reporting drug-related TEAEs according to the investigator's judgment was similar in the 2 treatment arms: 106 (35.2%) patients and 108 (35.9%) patients in the CT-P13 and Remicade treatment arms, respectively. The most frequently reported drug-related TEAEs (in ≥2% patients) were latent TB (CT-P13 arm: 4.3% vs. Remicade arm 4.7%), increased ALT (3.0% vs. 3.3%), increased AST (1.7% vs. 2.3%), RA (2.3% vs. 1.3%), nasopharyngitis (2.0% vs. 1.3%), urinary tract infection (1.3% vs. 2.3%), drug hypersensitivity (1.7% vs. 2.7%), infusion-related reaction (1.0% vs. 2.0%) and headache (1.3% vs. 2.0%).

The majority of TEAEs were of mild and moderate severity. Severe TEAEs were reported in a total of 25 (8.3%) patients in the CT-P13 arm and 21 (7.0%) patients in the Remicade arm. Only 3 TEAEs of severe intensity were reported in more than 1 patient in any treatment arm: asthenia, bone pain and RA.

- **Study CT-P13 1.1**

In the initial safety analysis, the number of patients reporting TEAEs was 83 (65%) in the CT-P13 arm and 78 (64%) in the Remicade arm. The most frequently TEAEs reported (in ≥5% patients in any treatment arm) included increased ALT (14.8% patients vs. 14.8% patients), increased AST (12.5% vs. 9.8%), increased blood creatine phosphokinase (CPK) (5.5% vs. 1.6%), headache (7.8% vs. 4.1%), nasopharyngitis (7.0% vs. 5.7%) and upper respiratory tract infection (3.1% vs. 7.4%). All TEAEs reported in ≥1% of patients in any treatment arm are summarised in the table below.

Table 40 Most common TEAEs in AS patients (≥1% of patients in any treatment arm)

System Organ Class Preferred Term (MedDRA)	Study CT-P13 1.1	
	CT-P13	Remicade®
	N=128	N=122
Total number of events (TEAEs)	250	263
Number of patients with at least 1 event (TEAE)	83 (64.8)	78 (63.9)
Drug-related	*57 (44.5)*	*58 (47.5)*
Blood and lymphatic system disorders	**5 (3.9%)**	**7 (5.7)**
Anaemia	1 (0.8)	3 (2.5)
Leukopenia	0	2 (1.6)
Neutropenia	2 (1.6)	2 (1.6)

System Organ Class Preferred Term (MedDRA)	Study CT-P13 1.1	
	CT-P13	Remicade®
	N=128	N=122
Cardiac disorders	**3 (2.3)**	**6 (4.9)**
Bradycardia	1 (0.8)	2 (1.6)
Eye disorders	**5 (3.9)**	**6 (4.9)**
Conjunctivitis	2 (1.6)	4 (3.3)
Gastrointestinal disorders	**17 (13.3)**	**13 (10.7)**
Abdominal pain	1 (0.8)	3 (2.5)
Diarrhoea	4 (3.1)	0
Dyspepsia	2 (1.6)	0
Gastritis	2 (1.6)	1 (0.8)
Gastrooesophageal reflux disease	1 (0.8)	2 (1.6)
Nausea	4 (3.1)	2 (1.6)
Toothache	2 (1.6)	1 (0.8)
Vomiting	2 (1.6)	1 (0.8)
General disorders and administration site conditions	**3 (2.3)**	**8 (6.6)**
Infusion-related reaction	0	3 (2.5)
Pyrexia	3 (2.3)	2 (1.6)
Immune system disorders	2 (1.6)	2 (1.6)
Drug hypersensitivity	2 (1.6)	1 (0.8)
Infections and infestations	**41 (32.0)**	**41 (33.6)**
Bacteriuria	1 (0.8)	2 (1.6)
Bronchitis	1 (0.8)	3 (2.5)
Cervicitis	0	2 (1.6)
Fungal infection	0	2 (1.6)
Influenza	0	5 (4.1)
Latent tuberculosis	5 (3.9)	4 (3.3)
Nasopharyngitis	9 (7.0)	7 (5.7)
Pharyngitis	3 (2.3)	4 (3.3)
Sinusitis	3 (2.3)	2 (1.6)
Tinea pedis	2 (1.6)	0
Tonsillitis	0	2 (1.6)
Upper respiratory tract infection	4 (3.1)	9 (7.4)
Urinary tract infection	6 (4.7)	0
Viral upper respiratory tract infection	2 (1.6)	1 (0.8)
Investigations	**29 (22.7)**	**26 (21.3)**
Alanine aminotransferase increased	19 (14.8)	18 (14.8)
Aspartate aminotransferase increased	16 (12.5)	12 (9.8)
Blood creatine phosphokinase increased	7 (5.5)	2 (1.6)
Blood lactate dehydrogenase increased	2 (1.6)	0
Blood phosphorus decreased	2 (1.6)	0
Gamma-glutamyltransferase increased	4 (3.1)	4 (3.3)
Hepatic enzyme increased	0	2 (1.6)
Transaminases increased	2 (1.6)	0
Weight increased	2 (1.6)	1 (0.8)
Musculoskeletal and connective tissue disorders	**14 (10.9)**	**11 (9.0)**
Ankylosing spondylitis	2 (1.6)	2 (1.6)
Arthralgia	3 (2.3)	1 (0.8)
Back pain	0	3 (2.5)
Muscle spasms	2 (1.6)	0
Pain in extremity	2 (1.6)	0
Temporomandibular joint syndrome	2 (1.6)	0
Nervous system disorders	**17 (13.3)**	**11 (9.0)**
Dizziness	4 (3.1)	1 (0.8)
Headache	10 (7.8)	5 (4.1)

System Organ Class Preferred Term (MedDRA)	Study CT-P13 1.1	
	CT-P13	Remicade®
	N=128	N=122
Respiratory, thoracic and mediastinal disorders	**4 (3.1)**	**9 (7.4)**
Oropharyngeal pain	2 (1.6)	1 (0.8)
Rhinitis allergic	0	2 (1.6)
Skin and subcutaneous tissue disorders	**12 (9.4)**	**14 (11.5)**
Dermatitis allergic	1 (0.8)	2 (1.6)
Pruritus	3 (2.3)	0
Pruritus generalised	2 (1.6)	0
Rash	0	4 (3.3)
Urticaria	0	2 (1.6)
Vascular disorders	**4 (3.1)**	**1 (0.8)**
Hypertension	3 (2.3)	1 (0.8)

The proportion of patients reporting drug-related TEAEs was similar in the 2 treatment arms: 57/128 (44.5%) and 58/122 (47.5%) in the CT-P13 and Remicade arm, respectively. The most frequently reported drug-related TEAEs (in ≥2% patients) were increased ALT (CT-P13 arm: 9.4% vs. Remicade arm: 9.0%), increased AST (8.6% vs. 6.6%), increased gamma-glutamyltransferase (GGT) (2.3% vs. 2.5%), blood CPK increased (3.1% vs. 0.8%), latent TB (3.9% vs. 3.3%), urinary tract infection (3.9% vs. 0%), nasopharyngitis (2.3% vs. 1.6%), pharyngitis (1.6% vs. 2.5%), upper respiratory tract infection (2.3% vs. 1.6%), pyrexia (2.3% vs. 1.6%), headache (2.3% vs. 0.8%), infusion-related reaction (0% vs. 2.5%) and rash (0% vs. 2.5%).

Most TEAEs were of mild to moderate severity. In the CT-P13 arm, 3 (2.3%) patients experienced 5 severe TEAEs compared to 6 (4.9%) patients in the Remicade arm experiencing 7 severe TEAEs. No severe TEAE was reported by more than 1 patient in either treatment arm except for increased GGT in 2 patients.

- **Study CT-P13 1.2**

The proportion of patients who experienced TEAEs was similar in the 2 treatment arms; 6 patients in the CT-P13 arm and 5 patients in the Remicade arm reported 16 and 18 TEAEs, respectively. Only hypersensitivity, dizziness and pruritus were observed in more than 1 patient (all in the Remicade arm).

Serious adverse events / deaths / other significant events

Deaths

No deaths were reported in any study up to week 30. In the updated safety analysis up to Week 54, three deaths were reported: 1 in the CT-P13 arm (after a traffic accident) and 2 in the Remicade arm (1 after a traffic accident and 1 sudden death).

Serious adverse events

- *Study CT-P13 3.1*

In the initial analysis, 30/301 (10%) patients in the CT-P13 arm and 21/301 (7%) patients in the Remicade arm experienced 35 SAEs and 22 SAEs, respectively. The most frequently reported SAEs were uveitis (CT-P13: 2 patients, 0.7% vs. Remicade: 0%), infusion-related reaction (1 patient, 0.3% vs. 4, 1.3%), disseminated TB (2 patients, 0.7% vs. 0%), and deep vein thrombosis (2 patients, 0.7% vs. 0%). No other SAEs were reported for more than 1 patient in either treatment arm. SAEs were considered drug-related in 17 (5.6%) patients in the CT-P13 arm and in 10 (3.3%) patients in the Remicade arm.

In the safety update up to Week 54, 42 (14%) patients in the CT-P13 arm and 30 (10%) patients in the Remicade arm experienced 49 SAEs and 38 SAEs, respectively.

- *Study CT-P13 1.1*

In the initial analysis, 9 patients experienced SAEs: 4/128 (3.1%) patients in the CT-P13 arm experiencing 5 SAEs and 5/122 (4.1%) patients in the Remicade arm experiencing 8 SAEs. Drug-related SAEs occurred in 3 (2.3%) patients receiving CT-P13 (TB and oesophageal perforation, disseminated TB, and dyspnoea in the third patient) and in 4 (3.3%) patients receiving Remicade(cellulitis and wound infection, infusion-related reaction, pulmonary TB, and infusion-related reaction).

In the safety update at Week 54; similar numbers of patients with SAEs were observed: 8 patients in each arm experienced 10 SAEs for the CT-P13 arm and 11 SAEs for the Remicade arm.

- *Study CT-P13 1.2*

One patient in the CT-P13 arm experienced 7 SAEs and 1 patient in the Remicade arm experienced 2 SAEs. Five of the 7 SAEs reported in the CT-P13 group were drug related: disseminated TB, sepsis, septic shock, hepatotoxicity, and pneumonia. The 2 remaining SAEs were not drug-related (pancreatitis and acute renal failure). All SAEs led to premature discontinuation from treatment. The 2 SAEs reported with Remicade were considered not drug related (hypotension and peptic ulcer).

Other significant events

- *Risk of infections*

In the initial analysis of Study CT-P13 3.1, the proportions of patients who experienced at least 1 TEAE of infection were similar in the CT-P13 and Remicade treatment arms (95 patients, 31.6% vs. 107 patients, 35.5%, respectively). The number of TEAEs was also similar: 141 and 149, respectively. The most frequent infections in the CT-P13 arm were latent TB (6.3%), nasopharyngitis (6.3%), urinary tract infection (4.3%), and upper respiratory tract infection (4.0%). In the Remicade arm, they were latent TB (6.0%), nasopharyngitis (5.0%), bronchitis (4.0%), and urinary tract infection (4.0%). No other infections were reported for more than 3% of patients in either treatment arm. The majority of these infections were considered to be unrelated to study treatment.

The safety update up to Week 54 also showed that the proportion of patients who experienced at least 1 TEAE of infection was similar between the treatment arms: 126 patients (41.7%) in the CT-P13 arm vs. 136 patients (45.3%) in the Remicade arm. The most frequent infections (≥ 5% patients) reported in the CT-P13 treatment arm were latent TB (8.9%), upper respiratory tract infection (8.9%), nasopharyngitis (7.9%), and urinary tract infection (6.0%). In the Remicade arm, they were latent TB (8.3%), urinary tract infection (7.0%), nasopharyngitis (5.7%), bronchitis (5.7%), and upper respiratory tract infection (5.3%).

In the initial analysis of Study CT-P13 1.1, TEAEs of infection were reported by 41 (32.0%) patients and 41 (33.6%) patients in the CT-P13 and Remicade treatment arms, respectively. The most frequent infections in the CT-P13 arm were nasopharyngitis (7.0%), urinary tract infection (4.7%), latent TB (3.9%), upper respiratory tract infection (3.1%), pharyngitis and sinusitis (2.3% each). In the Remicade arm, they were upper respiratory tract infection (7.4%), nasopharyngitis (5.7%), influenza (4.1%), latent TB (3.3%), and pharyngitis (3.3%).

At Week 54, the proportion of patients who experienced at least 1 TEAE of infection were similar between the treatment arms: 53 patients (41.4%) in the CT-P13 arm vs. 49 patients (40.2%) in the Remicade arm. The most frequent infections (more than 5% patients) in the CTP13 arm were nasopharyngitis

(9.4%), upper respiratory tract infection (7.8%), as well as latent TB and urinary tract infection (6.3% each). In the Remicade arm, they were upper respiratory tract infection (10.7%), nasopharyngitis (8.2%), and pharyngitis (5.7%).

In Study CT-P13 1.2, the proportion of patients who experienced at least 1 TEAE of infection was similar in the CT-P13 and Remicade treatment arms (4 patients, 44.4% vs. 3 patients, 33.3%, respectively).

Overall, in the safety update at Week 54, 18 serious infections were reported across all studies in 16 patients treated with CT-P13 vs. 12 in 10 in patients treated with Remicade; these included in particular active tuberculosis (6 vs. 1) and pneumonia (5 vs. 0). In total, 7 cases of active TB (including 3 disseminated TB) occurred in patients treated with CT-P13 (1.6%) vs. 1 case (0.2%) in patients treated with Remicade. However, it is noted that in the CT-P13 arm, four cases of TB did not fulfil adequate diagnostic criteria of tuberculosis and/or had pre-existing suspicious pulmonary lesions.

Table 41 Summary of infections in the whole clinical programme

	All reported cases		Excluding unconfirmed TB[5] or pneumonia cases with pre-existing risk factors[6]	
System Organ Class Preferred Term	CT-P13 (N=440)	Remicade® (N=431)	CT-P13 (N=437)	Remicade® (N=431)
No. of patients with at least one TEAE with infections[1]	185/440 (42.0%)	190/431 (44.1%)	NA	NA
No. of patients with at least one SAE with infections[1]	16/440 (3.6%)	10/431 (2.3%)	NA	NA
No. of SAE with infections (events)[1, 2]	18/440 (4.1%)	12/431 (2.8%)	13/437 (3.0%)	12/431 (2.8%)
Tuberculosis[3]	6/440 (1.4%)	1/431 (0.2%)	4/437 (0.9%)	1/431 (0.2%)
Pneumonia[3]	5/440 (1.1%)	0/431 (0%)	2/437 (0.5%)	0/431 (0%)
Sepsis[3]	1/440 (0.2%)	3/431 (0.7%)	NA	NA
Other infections[4]	6/440 (1.4%)	8/431 (1.9%)	NA	NA

1 All treatment emergent events
2 Among patients who developed SAEs, 1 patient from CT-P13 group has 3 events (tuberculosis, pneumonia and sepsis including septic shock in Study CT-P13 1.2; 1 patient from Remicade® group have 2 events (cellulitis and wound infection) in Study CT-P13 1.1; 1 patient from Remicade® group have 2 events (right renal abscess and septic shock) in Study CT-P13 3.1.
3 One patient from CT-P13 group has 3 events (TB, pneumonia and sepsis including septic shock).
4 Other infections include cellulitis, wound infection and appendicitis with Remicade® group in Study CT-P13 1.1; cellulitis, joint abscess, pyoderma, urinary tract infection, wound infection staphylococcal and gastroenteritis with CT-P13 group; two events of appendicitis, coxsackie myocarditis, herpes zoster and renal abscess with Remicade® group in Study CT-P13 3.1.
5 Patients who had unconfirmed TB at the time of diagnosis were excluded
6 Patients who had risk factors for pneumonia at baseline were excluded

- *Infusion-related reactions*

In the initial analysis of Study CT-P13 3.1, 16 (5.3%) patients in the CT-P13 arm and 18 (6.0%) patients in the Remicade arm experienced at least 1 TEAE due to the infusion of study medication. The total number of TEAEs reported was 20 in the CT-P13 arm (10 mild/7 moderate/3 severe) and 30 in the Remicade arm (15 mild/13 moderate/2 severe). TEAEs were serious in 4 /301 patients (1.3%) in each treatment arm and 9 (3.0%) patients in each treatment arm discontinued study treatment due to an infusion-related reaction.

In the initial analysis of Study CT-P13 1.1, 5/128 (3.9%) patients in the CT-P13 arm and 6/122 (4.9%) patients in the Remicade arm experienced an infusion-related reaction, respectively.

No infusion-related reaction occurred in Study CT-P13 1.2.

In the safety update at Week 54, infusion-related reactions were reviewed based on a more comprehensive definition; this analysis showed fewer infusion-related reactions to CT-P13 than Remicade. In Study CT-P13 1.1, 4 (3%) patients in the CT-P13 arm and 11 (9%) patients in the Remicade arm experienced hypersensitivity and infusion-related reactions. In Study CT-P13 3.1, 23 (8%) patients in the CT-P13 arm and 31 (10%) patients in the Remicade arm experienced hypersensitivity and infusion-related reactions. Serious infusion-related reactions including anaphylactic/anaphylactoid

reactions occurred in the same number of patients (7) in both treatment arms and led to treatment discontinuation. Furthermore, the same proportion of the affected patients (5 patients; 71%) was antibody-positive with higher NAb titres compared to the average of the safety population. The type, management and outcome of these reactions were also comparable between the treatment arms.

- *Other adverse events of special interest*

No heart failure, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders as well as lymphoproliferative disorders were reported in the 3 studies.

SAEs of hepatotoxicity were reported in 2 patients treated with CT-P13. Neutropenia occurred in 3 patients receiving CT-P13 and 2 patients receiving Remicade.

Cases of malignancies were observed in 1 patient treated with CT-P13 (renal neoplasm) and 3 patients treated with Remicade (breast, ovarian, skin).

Laboratory findings

In Study CT-P13 3.1, there were 38 CTCAE grade 3/4 laboratory results in the CT-P13 arm and 27 in the Remicade arm. The most common significant grade 3 (severe) abnormality was high GGT concentration (6 [2.0%] patients in each treatment arm). The most common grade 4 (life threatening) result was low total neutrophils level (4 [1.3%] patients and 3 [1.0%] patients in the CT-P13 and Remicade treatment arms, respectively).

In Study CT-P13 1.1, there were 26 CTCAE grade 3/4 laboratory results in the CT-P13 arm and 20 in the Remicade arm. Ten patients (6 and 4 patients in the CT-P13 and Remicade arms, respectively) had grade 4 results.

Immunological events

See immunogenicity in the PK section. The impact of antibody development on the efficacy and safety of CT-P13 and Remicade was further investigated during the procedure upon request of the CHMP.

In the RA study CT-P13 3.1, complete loss of efficacy (defined as loss of ACR20 response) was reported slightly more frequently with CT-P13 than Remicade: at Week 30, 14% vs. 10%, respectively, and at Week 54, 13% vs. 11%, respectively (PP population). In addition, slightly more patients discontinued CT-P13 treatment than Remicade (10 vs. 6) due to lack of efficacy. An opposite trend was reported in the AS study CT-P13 1.1: at Week 30, 5% vs. 9%, respectively, and at Week 54, 9% vs. 10%, respectively (All-randomised population).

The efficacy response (ASAS20, ACR20) and adverse reactions (hypersensitivity and infusion related reactions) were analysed by seroconversion status at Week 54. In study CT-P13 3.1, the response rates were higher in ADA-negative patients as expected but comparable between the two products in each seroconversion status subgroup. The ACR20 response rate in the seroconverted subgroup was 49.1% in the CT-P13 arm and 44.5% in the Remicade arm compared with 66.7% and 61.2%, respectively, in the non-seroconverted subgroup. In Study CT-P13 1.1, comparable ASAS20 response rates were observed in the non-seroconverted subgroup (74.0% vs. 71.1% in the CT-P13 and Remicade arms, respectively). In the seroconverted subgroup, a difference in the response rate was noted (48.3% in the CT-P13 arm vs. 65.6 % in the Remicade arm) but the number of patients in this subgroup was small.

The analysis of the safety data showed that the development of antibodies to infliximab was associated with an increase in the frequency of hypersensitivity/ infusion-related reactions in both treatment arms as indicated in the table below.

Table 42 Hypersensitivity / infusion related reactions by seroconversion status

		At Week 54		Up to Week 54
Seroconversion Subgroups	Treatment	ASAS20 in Study CT-P13 1.1 (All randomized pop.) n/N (%)	ACR20 in Study CT-P13 3.1 (All randomized pop.) n/N (%)	Hypersensitivity/Infusion-related reactions in Studies CT-P13 1.1 and CT-P13 3.1 (Safety pop.) n/N (%)
Seroconverted	CT-P13	14/29 (48.3)	82/167 (49.1)	23/212 (10.8)
	Remicade®	21/32 (65.6)	73/164 (44.5)	34/202 (16.8)
Non-Seroconverted	CT-P13	57/77 (74.0)	90/135 (66.7)	4/218 (1.8)
	Remicade®	54/76 (71.1)	85/139 (61.2)	8/219 (3.7)

Safety in special populations

No studies in special population were conducted.

Safety related to drug-drug interactions and other interactions

No studies for drug-drug interaction and other interactions were conducted.

Discontinuation due to adverse events

In the initial analysis of Study CT-P13 3.1, TEAEs leading to premature discontinuation from study treatment were reported in 29 (9.6%) patients in the CT-P13 arm compared to 26 (8.6%) patients in the Remicade arm, respectively. In the CT-P13 arm, the most frequently reported TEAEs leading to discontinuation were infusion-related reaction (3 patients, 1.0%), disseminated tuberculosis (2 patients, 0.7%), latent tuberculosis (2 patients, 0.7%), and ALT increased (2 patients, 0.7%). In the Remicade arm, these TEAEs were infusion-related reaction (5 patients, 1.7%), drug hypersensitivity (3 patients, 1.0%), and latent tuberculosis (4 patients, 1.3%).

In the initial analysis of study CT-P13 1.1, TEAEs leading to discontinuation were reported in 6 (4.7%) patients in the CT-P13 arm compared to 5 (4.1%) patients in the Remicade arm. In the CT-P13 arm, these TEAEs were: TB (active 2 and latent 1); increased ALT (1); paraesthesia (2), dyspnoea (1). These TEAEs were infusion-related reaction (3), pulmonary TB (1), myocardial infarction (1) in the Remicade arm.

In study CT-P13 1.2, TEAEs leading discontinuation from study treatment were reported in 2 patients in the CT-P13 arm and 1 patient in the Remicade arm.

In the safety update at Week 54 of the RA study CT-P13 3.1, TEAEs leading to premature discontinuation of study treatment were reported in 33 (10.9%) patients in the CT-P13 arm compared to 45 (15.0%) patients in the Remicade arm. In Study CT-P13 1.1, TEAEs leading to premature discontinuation of study treatment were reported in 10 (7.8%) patients in the CT-P13 arm compared to 9 (7.4%) patients in the Remicade arm. The TEAEs leading to treatment discontinuation were generally similar in both treatment arms, mainly infusion-related reactions and tuberculosis (latent or active).

Post marketing experience

There were no post marketing data submitted.

2.6.1. Discussion on clinical safety

In total, 871 patients were included in the safety population: 602 from Study CT-P13 3.1, 250 from Study CT-P13 1.1 and 19 from Study CT-P13 1.2. A safety update at 54 weeks after all patients had completed the comparative treatment phase of the trials was submitted as requested by the CHMP. Overall, 455 (75%) patients in the RA trial and 210 (84%) patients in the AS trial received the full treatment (9 infusions); this represents a safety database of 339 patients treated with CT-P13 for 1 year.

A long-term follow-up study in patients with refractory RA recently published (Delabaye & De Keyser 2010) found that the highest number of adverse reactions, including infections and infusion reactions, were reported during the first 26 weeks of treatment with infliximab; thereafter, their incidence decreased gradually over time. Thus, the main comparison of the safety profile of the two products in the initial safety analysis covering essentially the first 30 weeks of treatment is justified. In the two pivotal trials, the proportion of patients reporting TEAEs was similar in the 2 treatment arms: 60% in the CT-P13 arm vs. 61% in the Remicade arm in the RA trial and 65% vs. 64%, respectively, in the AS trial. The majority of TEAEs were of mild to moderate severity.

Overall, the type and incidence of TEAEs to CT-P13 and Remicade reported in the RA and AS trials appeared generally similar and in line with those expected on the basis of the Remicade SmPC; they reflect the pharmacodynamics and immunogenic properties of infliximab. The most common ADRs were infections, including tuberculosis (latent or active) and nasopharyngitis, increase in liver enzymes, infusion-related reactions, hypertension and headache.

Upon request of the CHMP, the Applicant further evaluated the vascular events, which overall occurred slightly more frequently with CT-P13 (29 patients; 6.7%) than with Remicade (17 patients; 4.0%), and especially hypertension (19 [4.4%] patients treated with CT-P13 vs. 11 [2.6%] patients treated with Remicade). The Applicant showed that more patients in the CT-P13 arm had a medical history of hypertension and/or other underlying conditions predisposing to hypertension compared to the Remicade arm. About 50% of the cases in the CT-P13 arm occurred in patients with known ongoing hypertension, and importantly, the number of patients with new-onset of hypertension was similar in both treatment arms (10 vs. 9). Most events of hypertension, which is known to be highly prevalent in RA, were mild to moderate in severity; they occurred mainly during the initial phase of therapy (i.e. up to Week 22). Other vascular events included thrombophlebitis (superficial or deep) in 4 patients in the CT-P13 arm vs. 3 in the Remicade arm and venous insufficiency in 3 patients vs. 1, respectively. Overall, the CHMP concluded that the detailed analyses presented did not indicate any unexpected safety signal of vascular event, in particular hypertension, with CT-P13.

It is well known that antibodies to infliximab may induce a decrease in therapeutic response and loss of efficacy. Data from the two clinical trials are consistent with this finding; for example, the overall ACR20 response rate at Week 54 was 47% in patients that had seroconverted compared with 64% in patients that remained antibody-negative. However, importantly, the impact of the immune response was comparable in the CT-P13 and Remicade arms, with a difference of about 17 points between the response rates of seropositive and seronegative patients. A higher risk of infusion reactions was also found in the patients that seroconverted during the studies (13.8%) than in those that remained antibody-negative (2.7%), with more infusion-related reactions reported with Remicade than CT-P13. Likewise, the influence of antibodies was similar in both treatment arms, with a 4.5- to 6-fold increase in reaction rates in the presence of antibodies. Overall, these analyses demonstrate that the impact of antibodies against infliximab on the efficacy and safety of CT-P13 or Remicade is comparable.

The main safety concern raised during the procedure related to a slightly higher incidence of SAEs under CT-P13 than under Remicade in the RA trial: in the safety update at Week 54, 42 (14%) patients in the CT-P13 arm and 30 (10%) patients in the Remicade arm experienced 49 SAEs and 38 SAEs, respectively. The numerical imbalance was mainly due to an excess of infections and vascular disorders. In the AS trial, the incidence of SAEs was the same in both treatment arms.

In the whole database across trials, the overall numerical imbalance in patients with serious infectious events (16 vs. 10) was essentially driven by an imbalance in cases of active tuberculosis (6 vs. 1; in total, 7 cases vs. 1) and pneumonia (5 vs. 0). For the latter, the Applicant referred to an imbalance of risk factors for pneumonia in the medical history (chronic bronchitis or emphysema, and uncontrolled

diabetes mellitus) between the treatment arms. The Applicant further discussed in details the potential safety signal of tuberculosis and impaired host defence with a range of arguments as follows.

- In the CT-P13 arm, four cases of TB did not fulfil adequate diagnostic criteria of tuberculosis and/or had pre-existing suspicious pulmonary lesions.
- The total rate of infections was comparable in both treatment arms: 42% in patients receiving CT-P13 vs. 44% in patients receiving Remicade. No other opportunistic infections were identified and observed malignancies were equally distributed across the treatment arms.
- The TB rate in patients treated with CT-P13 (1.6%) was comparable to those reported in historical RA studies (0.6%, range of 0% - 1.2%) and AS studies (0.8%, range of 0% - 5%) with Remicade whereas it was unexpectedly low in patients treated with Remicade (0.2%).
- Seroconversion in the interferon-gamma release assay was equally frequent in both treatment arms: 23% in each arm of the AS trial and 20% (CT-P13) vs. 19% (Remicade) in the RA trial.
- There is no plausible explanation for a difference in host defence from a mechanistic point of view considering the difference in glycosylation detected in the Fc region of the two products. Lower ADCC would result in reduced cytolysis of T cells, monocytes and macrophages, conferring less inhibition of host defence. Moreover, the risk of TB seems mainly mediated by the Fab region as certolizumab, an anti-TNF devoid of Fc region, appears to display a similar risk of TB as the intact anti-TNF antibodies.

Based on the totality of the evidence presented, the CHMP concluded that the difference observed in the clinical programme was likely to be a chance finding.

As described in the RMP, the Applicant will further follow-up the risk of serious infections including TB as part of several registries in South Korea and the EU enrolling patients with rheumatoid arthritis and inflammatory bowel diseases. The Applicant will provide annual reports on these registries until 2026. Long term safety, including risk of infection and TB, is further monitored in an ongoing Korean post-marketing surveillance study in all adult infliximab indications. Additional safety data will also be provided from planned and ongoing comparative studies and extension studies open to patients recruited in the initial studies.

2.6.2. Conclusions on the clinical safety

The size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of CT-P13. The TEAEs patterns observed in the clinical studies were generally similar between the CT-P13 and the Remicade arms and appeared also in line with the well-characterised safety profile of Remicade as outlined in its SmPC.

A numerical imbalance in serious adverse events was observed in the RA pivotal trial CT-P13 3.1 with a higher incidence of serious infections, including active tuberculosis. However, the numbers involved are small and a thorough review of all available data suggests that the observed difference was most likely a chance finding. Serious infections, including tuberculosis will be closely monitored on a longer term and in larger patient cohorts as part of post authorisation measures through registries as described in the RMP. Rare adverse reactions known to Remicade, such as malignancies and lymphoproliferative disorders, will also be closely monitored as part of these registries.

Detailed analyses of serious infusion-related reactions, including anaphylactic reaction, and vascular disorders, especially hypertension, did not indicate any unexpected safety signal for CT-P13.

Finally, an extensive analysis of the immunogenicity profile of CT-P13 has been conducted in the clinical trials, which demonstrates that the immune response to infliximab and its impact on safety and efficacy is comparable between CT-P13 and Remicade.

2.6.3. Extrapolation of efficacy and safety

The CHMP guideline on biosimilar monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) states that extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification.

The Applicant provided a review of the literature on the role of TNFα in the disorders covered by the therapeutic indications of Remicade and the potential mechanisms of action of the various anti-TNFs. The mechanism of action of infliximab is complex; many questions remain unanswered and new insights into this mechanism should emerge in the future. The primary mode of action results from direct blocking of TNF receptor-mediated biological activities. Infliximab binds to soluble (s) or transmembrane (tm) TNF, thereby blocking their capacities to bind TNFR1 or TNFR2 and hence preventing cellular functions such as cell activation, cell proliferation, cytokine and chemokine production, which in turn inhibits cell recruitment, inflammation, immune regulation, angiogenesis, and extracellular matrix degradation. Several other potential mechanisms are induced by the binding of infliximab to tmTNF and include reverse signalling (inducing apoptosis or cytokine suppression) or cytotoxicity of the tmTNF-bearing cell by CDC or ADCC. While binding to s and tmTNF involves the Fab region of infliximab, the latter mechanisms involve binding of the molecule to complement or effector cells through its Fc region.

It is currently believed that neutralisation of sTNF and tmTNF is responsible of its efficacy in RA by preventing TNF from inducing TNFR-mediated cellular functions. It can also be accepted that the effects of infliximab blockade on synovial inflammation are comparable in different forms of arthritis. Such effects are also believed to play a role in psoriasis plaques. However, more mechanisms are likely involved in inflammatory bowel diseases (IBD), which are related to its binding to tmTNFα and include reverse signalling and Fc-related effector functions. The relative contribution of these various effects is currently unknown.

The results of the extensive comparability exercise performed by the Applicant show that the only difference between CT-P13 and Remicade is a lower amount of afucosylated species, which results in lower binding to FcγRIIIa and hence lower ADCC activity in the most sensitive experimental *in vitro* model using NK cells of patients suffering from Crohn disease (CD) and with high affinity genotypes (V/V and V/F).

Minor quality differences are expected to be observed between a biosimilar and its reference product and the CHMP guideline states that the studies should be planned with the intention to detect any potential differences between biosimilar and reference medicinal product and to determine the relevance of such differences, should they occur.

A range of arguments and experiments enable to conclude with a high level of probability that the quality differences detected in the level of afucosylation and binding to FcγRIIIa are not clinically relevant.

- In blood, the physiological environment, the differences in binding to FcγRIIIa and in ADCC activity are abolished. This has been shown by repeating the experiments in the presence of serum of a CD patient, by using peripheral blood mononuclear cells preparations (rather than isolated NK cells) or by using whole blood. The difference in binding affinity is overcome by competition from plasma IgGs, soluble factors, immune complexes and the presence of mixed cell populations expressing multiple

FcRs. At inflammatory sites, the vascular permeability is increased, which allows for many blood components to enter the extravascular space.

- In a system representative of the inflammatory focus *in vivo* using LPS-stimulated monocytes as target cells and PBMCs as effector cells, no ADCC response is detected with either products and regardless of the donor cells used (healthy volunteer or CD patient). Indeed, LPS-stimulated monocytes express much lower levels of tmTNFα compared with transfected Jurkat cells and these are not sufficient to elicit an effective ADCC response. This means that ADCC is likely to be limited in inflammatory settings *in vivo*. It is acknowledged that to date, there are no published reports describing the induction of ADCC by TNF antagonists in a patient.
- Infliximab has been recently shown to induce a subset of regulatory macrophages (regMø) that has been postulated to promote gut mucosal wound healing in IBD. This model reflects the ability of infliximab to bind to macrophages (which express both FcγRI and FcRIIIa) through its Fc region and to activated T-cells expressing tmTNFα through its Fab region. Upon this binding, a distinct macrophage subset is induced with immunosuppressive capacities, including the production of anti-inflammatory cytokines and inhibition of T-cell proliferation. In this experiment using mixed lymphocyte reaction from FcγRIIIa genotype matched PBMCs (either healthy donors or CD patients), no differences in the proportion of regulatory macrophages induced and in the inhibition of T-cell proliferation can be detected between CT-P13 and Remicade, regardless of the FcγRIIIa genotype of the donor cells. This indicates that the difference in binding affinity does not affect the induction of regulatory macrophages. Furthermore, the monocyte/macrophages (including regMø) induced by CT-P13 or Remicade show the same ability to promote healing of an artificial wound made in a culture of colon epithelial cells.

In addition to these experiments intended to compare Fc-related functions of CT-P13 and Remicade, an *in vitro* model relevant to IBD intended to compare Fab-related functions has been presented, which uses a human intestinal epithelial cell line). The data show a dose-dependent suppression of cytokine secretion from human epithelial cells stimulated by a mixture of stimulators and this effect is comparable with both products. Likewise, CT-P13 and Remicade are similarly able to suppress apoptosis of human epithelial cells by blocking soluble TNFα.

In conclusion, by using a range of experimental models that are considered representative of the pathophysiological conditions and putative mechanisms of action of infliximab, the Applicant has provided convincing evidence that the difference detected in the amount of afucosylated species has no clinically relevant impact on the efficacy and safety of CT-P13, in particular in IBD. Additional *in vitro* data from human intestinal cells are further supporting extrapolation of the clinical data to IBD.

Extrapolation to IBD of the clinical data collected in AS is further supported by increasing genetic and immunological evidence of a clinical and histological overlap between gut inflammation in spondyloarthropathies and CD. Arthritis occurs in 9%-53% of patients with IBD and subclinical gut inflammation has been described in up to two-thirds of patients with spondyloarthropathies, with histologic gut inflammation found in 30%-60% of cases.

Finally, preliminary clinical data from a very small cohort of 23 patients with CD (15) or UC (8) indicate similar response to CT-P13 compared with historical data on Remicade. The Applicant has extended the enrolment of IBD patients in this post-marketing surveillance study and will conduct an additional comparative trial versus Remicade in active CD.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.3, the PRAC considers by consensus decision that the risk management system for infliximab (Remsima) is acceptable.

The PRAC also recommends that the Applicant could further consider participation in other available European databases with RA patients (e.g. in Sweden and Spain).

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 43 Summary of the safety concerns

Important identified risks	HBV reactivation
	Congestive heart failure
	Opportunistic infections
	Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
	Tuberculosis
	Serum sickness (delayed hypersensitivity reactions)
	Haematologic reactions
	Systemic lupus erythematosus/lupus-like syndrome
	Demyelinating disorders
	Lymphoma (not HSTCL)
	Hepatobiliary events
	Hepatosplenic T cell lymphoma (HSTCL)
	Intestinal or perianal abscess (in Crohn's disease)
	Serious infusion reactions during a re-induction regimen following disease flare
	Sarcoidosis/sarcoid-like reactions
	Paediatric malignancy
	Leukaemia
Important potential risks	Malignancy (excluding lymphoma)
	Colon carcinoma/dyplasia (in ulcerative colitis)
	Skin cancer
	Pregnancy exposure
	Infusion reaction associated with shortened infusion duration (in RA)
	Bowel stenosis, stricture, obstruction (in Crohn's disease)
Missing information	Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis, or psoriasis
	Long-term safety in children with Crohn's disease and ulcerative colitis
	Long-term safety in children
	Safety in very young children (<6 years)
	Use of infliximab during lactation
	Lack of efficacy
	Hypersensitivity

- **Pharmacovigilance plans**

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
Study CT-P13 1.2: A randomized, double-blind, parallel-group, Phase 1 study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Philippines)	3.0	Final	Week 30 data submitted in February 2012	September 2013
Study CT-P13 1.3: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 in patients with ankylosing spondylitis who were treated with Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 (Global)	2.0	Final	Not planned	December 2013
Study CT-P13 3.2: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 when co-administered with methotrexate in patients with rheumatoid arthritis who were treated with infliximab (Remicade or CT-P13) in Study CT-P13 3.1 (Global)	2.0	Final	Not planned	December 2013
Study CT-P13 3.3: Phase 3study to demonstrate equivalence in efficacy and safety of CT-P13 Compared With Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Russia)	1.0	Final	December 2013 (week 30)	August 2014
Study B1P13101: Double-blind, Parallel-group, Comparative study of CT-P13 and Remicade in Treatment of Patients with Rheumatoid Arthritis (Japan)	7.0	Final	Not planned	September 2013
Study B2P13111:Extension Study of the Phase I/II Clinical Study of CT-P13 in Treatment of Patients with Rheumatoid Arthritis (Japan)	3.0	Final	Not planned	February 2015
Registry CT-P13 4.2: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima in Patients with Rheumatoid Arthritis (EU and Korea)	Synopsis	Draft	Annual Safety and Efficacy Interim Analysis(data cut off December; reporting May) Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients) 2 year CSR: May 2023	May 2026
Post Marketing Surveillance of REMSIMA 100 mg (Infliximab) (Monoclonal antibody,,recombinant DNA product) to Evaluate Safety and Efficacy in Korea.	1.0	Final	Annual Special Interest report(TB and other serious infection)with PSUR Pooled TB and other	October 2016

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
			serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients) -March 2013 (6 month data) -September 2013 (1 year data) -March 2014 (1.5 year data) -September 2014 (2 year data) -September 2015 (3 year data)	
British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK)	1.0	Final	Interim analyses will be undertaken at appropriate time intervals. Such analyses will be a guide to the ultimate levels of recruitment and length of follow-up required Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients)	March 2026
Registry CT-P13 4.3: An observational, prospective cohort study to evaluate the safety and efficacy of Remsima in patients with Crohn's disease (CD), and Ulcerative Colitis (UC) (EU and Korea)	Synopsis	Draft	Annual Safety and Efficacy Interim Analysis (data cut off December; reporting May) Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients)	May 2026

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
Study CT-P13 3.4: A Randomized, Double-Blind, Parallel-Group, Phase 1/3 Study to Demonstrate Comparable Efficacy, Pharmacokinetic Profile, and Safety of CT-P13 to Remicade in Patients with Active Crohn's Disease (Global)	Synopsis	Draft	- May 2015 (6 week) - October 2015 (30 week)	June 2016
Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis (Germany):	Synopsis	Draft	Discussion on interim reports is ongoing Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients)	March 2026

The PRAC agreed with the proposed PhV plan but recommended that the Applicant could further consider participation in other available European databases with RA patients (e.g. in Sweden and Spain).

- **Risk minimisation measures**

Safety concern	Proposed risk minimisation activities (routine and additional)
Important Identified risks	
HBV reactivation	Routine: Labelling Additional: -Patient Alert Card -Educational material for HCPs.
Congestive heart failure	Routine: Labelling Additional: -Patient Alert Card -Educational material HCPs.
Opportunistic infections	Routine: Labelling Additional: -Patient Alert Card -Educational material HCPs.
Serious infections – including sepsis (excluding opportunistic infection and TB)	Routine: Labelling Additional: -Patient Alert Card -Educational material HCPs.
Tuberculosis	Routine: Labelling Additional: -Patient Alert Card -Educational material HCPs
Serum sickness (delayed hypersensitivity reactions)	Routine: Labelling Additional: -Educational material HCPs
Haematologic reactions	Routine: Labelling

Safety concern	Proposed risk minimisation activities (routine and additional)
Systemic lupus erythematosus/lupus-like syndrome	Routine: Labelling
Demyelinating disorders	Routine: Labelling
Lymphoma (not HSTCL)	Routine: Labelling Additional: -Educational material HCPs
Hepatobiliary events	Routine: Labelling
HSTCL	Routine: Labelling Additional: -Educational materials for HCPs
Intestinal and perianal abscess (in Crohn's disease)	Routine: Labelling
Serious infusion reactions during a re-induction regimen following a disease flare	Routine: Labelling Additional: -Educational materials HCPs
Sarcoidiosis/sarcoid-like reactions	Routine: Labelling
Paediatric malignancy	Routine: Labelling Additional: -Educational materials HCPs
Leukaemia	Routine: Labelling
Important potential risks	
Malignancy (excluding lymphoma)	Routine: Labelling
Colon carcinoma/dysplasia (in ulcerative colitis)	Routine: Labelling
Skin cancer	Routine: Labelling
Pregnancy exposure	Routine: Labelling
Infusion reaction associated with shortened infusion duration (in RA)	Routine: Labelling
Bowel stenosis, stricture, obstruction (in Crohn's disease)	Routine: Labelling
Missing information	
Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis, or psoriasis	Routine: Labelling
Long-term safety in children with Crohn's disease and ulcerative colitis	Routine: Labelling
Long-term safety in children	Routine: Labelling
Safety in very young children (<6 years)	Routine: Labelling
Use of infliximab during lactation	Routine: Labelling
Lack of efficacy	Routine: Labelling
Hypersensitivity	Routine: Labelling

The CHMP endorsed this advice without changes.

2.9. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Remicade. The bridging report submitted by the Applicant has been found acceptable by the CHMP.

3. Benefit-Risk Balance

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient *per se* as this has been shown for the reference product. The benefits and risks are inferred from the

similarity of the test product to the reference product in terms of quality, efficacy and safety. The purpose of a biosimilar application is to demonstrate similarity to the reference product.

Benefits

Beneficial effects

From a quality and non-clinical perspective, it is considered that similarity between CT-P13 and Remicade was shown with regard to:

- the primary and secondary structures of the infliximab molecule, and more specifically, the 3-D structure of the Fc domain;
- most of the glycosylation profile and degradation profile;
- the binding affinity to soluble monomeric and trimeric forms and to transmembrane TNFα;
- the activities related to binding to soluble TNFα (TNFα neutralisation, suppression of cytokine secretion and apoptosis in stimulated intestinal cells) and binding to transmembrane TNFα (apoptosis of cells overexpressing tm TNFα);
- the binding affinity to the complement component C1q, to Fcγ receptors RIa, RIIa and RIIb, and to FcRn;
- the binding affinity to Fcγ receptor RIIIb using the native receptors on polymorphic neutrophils (despite a difference detected by SPR, similar to that observed for FcRIIIa);
- the activities involving the Fc region: CDC assay, induction of regulatory macrophages and their effects (suppression of T-cell proliferation, wound healing of colorectal epithelium cells).

From a clinical perspective:

- The pivotal PK trial in patients with AS showed comparable PK profile at steady state with 90% confidence intervals for the ratios of both primary parameters (C_{max} and AUC) ranging between 93% and 116%, well contained within the standard bioequivalence interval of 80% – 125%;
- The pivotal efficacy trial in patients with rheumatoid arthritis achieved its primary endpoint since the 95% confidence interval for the difference in ACR20 was contained within the predefined equivalence margin (± 15%) in both the all-randomised and PP populations;
- PK data from the efficacy trial and efficacy data from the PK trial were also supportive of similarity.

Uncertainty in the knowledge about the beneficial effects

From a quality/non-clinical perspective, some differences were observed between CT-P13 and Remicade.

- There is less intact IgG in the CT-P13 product, mainly due to a higher proportion of non-assembled form. However, the difference is so small that it is unlikely to impact its biological activity as reflected by comparable TNFα binding affinity and potency.
- CT-P13 exhibits a higher level of C-terminal lysine variability (fewer isoforms with 2 C-terminal lysine residues and more isoforms with no C-terminal lysine). However, biological activity does not differ between these isoforms, and in any case, rapid cleavage of the C-terminal lysine occurs in blood.
- There is a slightly higher level of aggregates in the CT-P13 product than in Remicade, which could potentially increase immunogenicity. However, this risk is considered to be negligible given the very low level and is not reflected in the clinical data.

- CT-P13 exhibits a lower level of afucosylated glycans, hence a lower binding affinity to FcγRIIIa and a lower activity in the most sensitive ADCC assay using NK cells as effector cells and tmTNFα Jurkat target cells. However, no difference could be detected in several experiments that are more representative of pathophysiological conditions, and therefore, more relevant clinically (e.g. in blood, in a mixed lymphocyte reaction from FcγRIIIa genotype matched PBMCs with induction of a subset of regulatory macrophages, in a wound healing model using induced cells that include these macrophages on a culture of human colorectal epithelium cells).

From a clinical perspective:

- The efficacy of CT-P13 in RA was clearly shown to be non-inferior to that of Remicade. While the ACR20 results were numerically in favour of CT-P13, especially at Week 14, the 95% CIs of the treatment differences remained confined within the predefined equivalence margin of ±15%. Moreover, no such trend was observed in the AS trial.

Risks

Unfavourable effects

The safety profile of CT-P13 was supported mainly by the results from studies CT-P13 3.1 and CT-P13 1.1. The type and incidence of ADRs observed with CT-P13 and Remicade in the respective studies were generally similar and in line with those expected on the basis of the Remicade SmPC.

There were no marked differences in the immunogenicity profile of CT-P13 and Remicade up to 54 weeks and the impact of antibodies on efficacy and safety was comparable.

Uncertainty in the knowledge about the unfavourable effects

A numerical imbalance in patients with serious infections (16 vs. 10), including active tuberculosis, was observed with CT-P13 in comparison with Remicade. Based on a detailed analysis of these cases and further discussion by the Applicant about potentially impaired host defence, this difference is considered to be likely a chance finding. Serious infections, including TB will be closely monitored on a longer term and in larger set of population as part of registries as described in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Minor quality differences are expected to be observed between a biosimilar and its reference product; they are acceptable as long as they do not impact efficacy and safety.

All major physicochemical characteristics and biological activities of CT-P13 are comparable to those of Remicade except for a lower amount of afucosylation species, which translates in a lower binding affinity to FcγRIIIa receptor. This difference is not considered clinically relevant as it does not affect the activities of CT-P13 in the experimental models that are most relevant to the pathophysiological conditions. Furthermore, the contribution of ADCC to the mode of action of infliximab, or any TNF antagonist, has not been established in patients and ADCC may be limited in inflammatory focus *in vivo,* as illustrated by a model using LPS-stimulated monocytes as target cells and PBMCs as effector cells (no ADCC response detected with either products and regardless of the donor cells used, healthy volunteer or CD patient). Indeed, LPS-stimulated monocytes express much lower levels of tmTNFα compared with transfected Jurkat cells and these levels are probably not sufficient to elicit an effective ADCC response.

In two clinical trials, the pharmacokinetics, efficacy, safety, and immunogenicity profiles of CT-P13 are similar to those of Remicade.

The numerical difference observed in serious infections, and particularly active tuberculosis, is likely to be a chance finding. Indeed, the relevance of this finding is questionable due to lack of adequate diagnosis of tuberculosis or pre-existing suspicious pulmonary lesions in a few tuberculosis cases. Moreover, other infections, seroconversion in the interferon-gamma release assay, and malignancies are equally distributed across the treatment arms. Finally, there is no plausible explanation for a difference in host defence from a mechanistic point of view as the risk of tuberculosis seems mainly mediated by the Fab region of infliximab. The Applicant will closely monitor the serious infections as part of registries as detailed in the RMP.

Benefit-risk balance

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

Discussion on the benefit-risk balance

In a sensitive clinical model, the efficacy of CT-P13 was shown to be equivalent to that of Remicade. The general safety profile of CT-P13 was also shown to be comparable to that of Remicade and consistent with its SmPC. Additional data will become available to further characterise the long-term safety of CT-P13, including serious infectious events and tuberculosis, from the registries as well as the post-marketing studies as described in the RMP.

Extrapolation of the pharmacokinetic, efficacy and safety data generated in the two clinical trials in RA and AS to the other indications of Remicade, including IBD, is considered possible based on the results of the extensive *in vitro* and *ex vivo* comparability data on all functionalities of the infliximab molecule, including several experiments especially relevant to IBD. It is further supported by increasing genetic and immunological evidence of a clinical and histological overlap between gut inflammation in spondyloarthropathies and CD. Finally, preliminary clinical data from a small cohort of South Korean patients with CD and UC indicate similar response to CT-P13 compared with historical data on Remicade. Post-authorisation registries and studies, including a comparative trial vs. Remicade in active CD as detailed in the RMP, will provide further efficacy data in the treatment of IBD.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Remsima in the treatment of rheumatoid arthritis, adult Crohn's disease, paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit

periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall develop an educational programme for Remsima to include paediatric Crohn's disease and paediatric ulcerative colitis patients to ensure that physicians who intend to prescribe Remsima to these patients are aware of:

- The risk of opportunistic infections and tuberculosis (TB) in patients treated with Remsima.
- The need to assess the risk of TB in patients prior to treating with Remsima.
- The risk of acute infusion related reactions and delayed hypersensitivity reactions.
- The risk of lymphoma and other malignancies.
- The patient alert card, which is to be given to patients using Remsima.
- That children may be at at increased risk of developing infections and the need for immunisations to be up to date.

These conditions fully reflect the advice received from the PRAC.