Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Certolizumab pegol

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

February 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Biological Entity
Decision:	Approved
Date of decision:	22 December 2009
Active ingredient(s):	Certolizumab pegol
Product name:	Cimzia
Sponsor's name and address:	UCB Australia Pty Ltd Level 1, 1155 Malvern Road MALVERN VIC 3144
Dose form:	Solution for injection
Strength:	200 mg/mL
Container:	Graduated 1 mL glass Pre-Filled Syringe (PFS) with staked stainless steel needle closed using a fluoropolymer coated bromobutyl rubber stopper
Pack size:	Two pre-filled syringes per carton
Approved therapeutic use:	Cimzia is indicated for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. · combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDS) or · as monotherapy in case of a contraindication or intolerance to MTX (see Dosage and Administration).
Route of administration:	Subcutaneous Injection
Dosage:	400 mg (2x200 mg sub-cutaneous injections) at weeks 0, 2, and 4 followed by 200 mg every two weeks via sub-cutaneous injections

Product background

The sponsor applied to register certolizumab pegol for the treatment of adult patients with moderate to severely active rheumatoid arthritis (RA) who are either intolerant of methotrexate (MTX) or failed to adequately respond to conventional disease-modifying antirheumatic drugs (DMARDs) (including MTX). The sponsor requested that certolizumab pegol be approved for use in combination with MTX, or alone when continued treatment with MTX is inappropriate.

Cimzia (certolizumab pegol) is a recombinant, humanized, antibody Fab fragment with specificity for human tumour necrosis factor (TNF). The Fab fragment is manufactured in an E.coli bacterial expression system, subsequently purified, and conjugated via a maleimide group to polyethylene glycol (PEG). The chemical is presented as a clear, colourless, sterile solution in single use, pre-filled syringes containing 200 mg/mL of certolizumab pegol. The inactive ingredients are sodium chloride, sodium acetate (10 mM acetate, pH 4.7) and water. The chemical is administered by subcutaneous injection. The proposed dosing regimen is 400 mg at weeks 0, 2 and 4 of therapy, followed by 200 mg every 2 weeks thereafter. An alternative proposed maintenance dosing regimen is 400 mg every 4 weeks.

Status in other countries at the time of submission

A similar application has been approved in the European Union (1 October 2009); the USA (13 May 2008) and Canada (12 August 2009).

EU

On 15 November 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for Cimzia 200 mg powder and solvent for solution for injection, intended for the treatment of severe, active Crohn's disease. The CHMP was concerned that there was insufficient evidence to show a benefit of Cimzia. In the study of induction treatment, Cimzia showed only marginal effectiveness. Also, the study of maintenance treatment did not last long enough to give meaningful information on the medicine's long-term effects.

The CHMP was also concerned over Cimzia's safety. Although generally its safety was comparable with that of other medicines in the same class, there was some concern over a possible increased risk of bleeding in patients receiving Cimzia. Also, the CHMP was concerned that the company had not demonstrated that it would have been able to monitor the quality of the medicine to an acceptable level.

In March 2008, following a re-examination requested by the sponsor, the CHMP removed its concern regarding the ability to monitor the medicine's quality. It also removed its concern over the possible increased risk of bleeding but maintained a general concern over Cimzia's safety. The concerns about efficacy in Crohn's disease remained.

Marketing authorisation was approved on 1 October 2009 for the following indications:

Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

USA

On 22 April 2008, Cimzia was approved by the US FDA for the following indication:

Cimzia is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

On 13 May 2009, Cimzia was approved by the US FDA for the following additional indication:

Cimzia is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA).

Canada

Cimzia was approved in Canada for the treatment of moderately to severely active rheumatoid arthritis in adult patients on 12 August 2009.

The application has been submitted to Switzerland and Turkey but is still pending. No application has been submitted in New Zealand. No applications have been withdrawn or rejected.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality findings

Introduction

Certolizumab pegol is an inhibitor of TNF-α, a key cytokine that up-regulates cellular adhesion molecules and chemokines, major histocompatibility complex (MHC) class I and class II molecules, and directs leukocyte activation. Overproduction of TNF-α plays a key role in the pathogenesis of rheumatoid arthritis causing synovial inflammation and proliferation in addition to degradation of articular cartilage and bone.

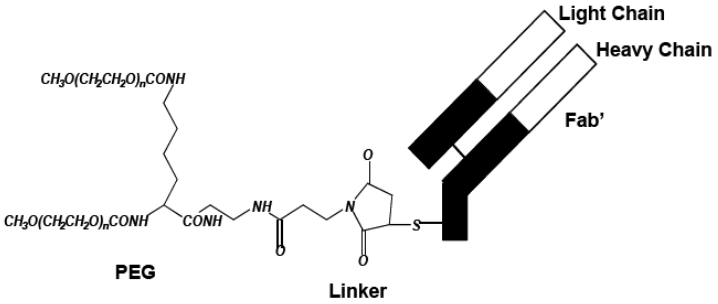
The formulation of the drug product is performed at the drug substance stage. The drug product manufacturing process comprises of thawing of the drug substance, compounding of the bulk drug product, two sterile filtration steps, filling and packaging.

CDP870 Drug Product is presented as a Solution for Injection in a graduated 1 mL glass Pre-Filled Syringe (PFS), containing 1 mL of 200 mg CDP870 in sodium acetate and sodium chloride. The pH of the solution is approximately 4.7.

Drug substance (active ingredient)

Structure and properties

The drug substance has the following structure:



The active substance of Cimzia, certolizumab pegol (CDP870 Drug Substance), consists of a preparation of purified recombinant, humanized Fab' antibody fragment (CDP870 Fab') covalently bound to PEG2MAL40K (PEG), a maleimido terminated bis methoxypoly (ethylene glycol) modified lysine. The Fab' fragment is manufactured in *E. coli*, purified, and conjugated via a maleimide group to polyethylene glycol (PEG) in order to extend its plasma half-life.

The humanized Fab' component of drug substance is of murine hybridoma origin, and expressed in Escherichia coli (E. coli). It comprises a light chain and heavy chain linked via a disulfide bond.

The PEG2MAL40K moiety is a polydisperse mixture of an average molecular weight of 41,000 Daltons (Da) that is covalently bound to the CDP870 Fab'.

The experimentally determined molecular mass of CDP870 Drug Substance is 90,428.8 Da

Nomenclature is described in the table below:

Table 3.2.S.1.1:1 CDP870 Drug Substance Nomenclature

Recommended International Nonproprietary Name (INN):	Certolizumab Pegol
Compendial Name:	Not applicable
Chemical Name(s):	gHTNF40 Fab'-40K PEG
Company or Laboratory Code:	Cimzia® CDP870 CDP870 Fab'-PEG Certolizumab Pegol CZP CDP870 Drug Substance PHA738144
Chemical Abstract Service (CAS) Registry Number:	428863-50-7
CAS Registry Name:	Immunoglobulin, anti-(human tumor necrosis factor alpha) Fab' fragment (human-mouse monoclonal CDP870 heavy chain), disulfide with human-mouse monoclonal CDP870 light chain, PEGylated heavy chain *immunomodulator*
USAN:	Certolizumab Pegol

Manufacture

The drug substance manufacturing for commercial batches is performed by Sandoz GmbH, Kundl, Austria.

Development genetics

The DNA sequences encoding the variable regions of the heavy and light chains (VH and VL) were derived from a hybridoma and inserted into an expression vector with OmpA as a signal peptide to direct secretion of CDP870 Fab' into the periplasmic space of E. coli (W3110).

Cell bank system

The cell bank system consists of a Master Cell Bank (MCB) and a Working Cell Bank (WCB) developed and maintained in accordance with GMP and ICH guidelines.

All manufacture of the drug substance is derived from the WCB. A single vial of MCB is used to generate each new WCB.

Procedures utilised in the in the preparation of the MCB and WCB have been appropriately described. An extensive range of tests has been performed for their characterisation in accordance with ICH guidelines, including purity, identity, stability and presence of adventitious agents.

Fermentation and purification processes

CDP870 Fab' is produced by fermentation of the E. coli production substrate. The CDP870 Fab' is extracted, purified, and PEGylated to form drug substance. The manufacturing process for the drug substance is divided into three main parts reflecting the major activities taking place during manufacture: fermentation, primary isolation and purification and modification reactions.

Manufacturing process and process controls for the drug substance manufacture are well described and adequate. Information on buffers, column regeneration and storage, and operating conditions has been provided.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Manufacturing process and process validation

The development of drug substance encompassed various site, scale and manufacturing process changes. The majority of the process changes had been associated with the primary recovery and downstream processing stages in an effort to increase the recovery of Fab', to increase the purity of the final drug substance, and to accommodate differences in various drug product formulations (e.g., protein concentration, final formulation buffer, pH).

There were nine process variations used for the manufacture of drug substance throughout development and scale-up, designated as Process 1 through Process 9 due to the aforementioned changes. In Process 6, 7 and 8, a lyophilised dosage form was developed to overcome hydrolysis of a polyethylene glycol (PEG) linker, the main degradation pathway in the liquid formulation. There were three manufacturing sites involved.

Process validation was based on validating the inputs into three consecutive drug substance batches. As a consequence of the batch pooling strategy, six fermentation and isolation batches were therefore included in the validation.

Results from all unit operations performed during drug substance manufacturing had been shown to consistently meet Critical Process Parameter and In-Process Acceptance Criteria ranges as appropriate and to produce CDP870 Drug Substance that meets its pre-

determined quality attributes, including control and removal product-related substance, product-related impurities and process-related impurities.

The process validation batches were also subjected to full release testing and all results met the proposed drug substance release specifications.

Characterisation

A comprehensive set of analytical methods have been employed to characterise the structure of the drug substance derived from Process 9.

The general properties of drug substance and CDP870 Fab' and its related species have been characterized based on size, charge and molecular mass, using SDS-PAGE under reducing and non-reducing conditions, Isoelectric Focusing and Mass Spectrometry techniques.

The primary structure and complete sequence for drug substance and CDP870 Fab' has been confirmed using amino acid analysis, peptide mass mapping, disulphide pairing, N-terminal sequencing and C-terminal clipping.

Higher order structural analysis was undertaken on drug substance and CDP870 Fab'. Secondary structure properties have been investigated by Circular Dichroism, Fourier Transform Infrared spectroscopy and Raman spectroscopy. The tertiary structure for CDP870 Fab' has been determined by X-Ray Crystallography.

The biological activity of the drug substance and CDP870 Fab' batches have been assessed using binding affinity using BIAcore surface plasmon resonance, binding to a TNF-α column and cell based potency assay.

Product-related substances for CDP870 Drug Substance have been characterized, including analysis of CDP870 Drug Substance (Fab'-PEG) isomers; amino acid modifications by oxidation and deamidation; acidic and basic species.

Product-related impurities have been identified and characterized to assure the quality of the drug substance. The characterized Product Related Impurities include Late Eluting Species, Aggregates, Methionine Oxidation, Fab' Species and Isomers.

Process-related impurities range from additives, such as antibiotics, antifoam, or reducing agents, to additives that are integral parts of the manufacturing system, such as endotoxin, DNA, Host Cell Proteins derived from the E. coli production substrate.

Specifications

The drug substance release specifications, including tests for identity, impurities, potency, quantity and general attributes are acceptable and well justified. Reference standards have been well described and qualified.

Stability

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

The stability data provided support the proposed shelf-life of the drug substance of 36 months from the date of final fill, stored at the intended storage condition of -70 ± 10°C.

Drug product

Formulation

CDP870 Drug Product is presented as a Solution for Injection, in a graduated 1 mL glass Pre-Filled Syringe (PFS), containing 1 mL of 200 mg CDP870 in 10 mM sodium acetate, 125mM sodium chloride, pH 4.7 (acetate buffer, pH 4.7).

The syringe is fitted with a staked 25G x ½" thin wall needle. The syringe is closed using a fluropolymer coated bromobutyl rubber stopper and a rigid needle shield consisting of an elastomeric needle cover and a polypropylene Rigid Needle Shield (RNS). In order to enhance patient usability, each syringe is presented pre-assembled with a plunger rod and pad, extended finger flange and barrel sleeve, and an RNS overcap. Each syringe is intended for single use.

Manufacture

The commercial drug product is manufactured at Vetter-Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany. The assembly, secondary packaging and labelling are performed at UCB S.A, Chemin du Foriest, Brainel'Alleud, Belgium.

The drug product manufacturing process consists of thawing of the drug substance, compounding of the bulk drug product, sterile filtration, preparation of primary packaging material, in-line sterile filtration and filling, visual inspection and bulk packaging. This is followed by assembly, secondary packaging and labelling at a different site.

The critical in-process controls and associated measurement methods for these processing operations are well described, adequate and acceptable.

The drug product manufacturing process has been validated through the execution of three consecutive batches covering the approximate minimum and maximum batch sizes. Parameters evaluated include in-process tests, in-process measurements such as mixing times and syringe performance and release testing. All predefined acceptance criteria were met and demonstrated that the established manufacturing conditions result in consistent and reproducible product characteristics.

Pharmaceutical development

During early clinical development, the dosage form and pH had undergone changes to improve the stability of the drug substance.

Development of a more patient friendly presentation of a liquid formulation led to a pre-filled syringe (PFS) format as the proposed commercial drug product for injection, 200 mg/mL (Pre-Filled Syringe), which is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG in Langenargen, Germany. The PFS has been used in the Phase III clinical program.

Overall there have been three phases of manufacture development and a total of seven process variations used for the manufacture of drug product throughout development and scale-up, designated as Process 1 through Process 7 (the commercial process).

Specifications

The final product release and shelf-life specifications, including tests for identity, impurities, potency, quantity and general attributes, are well justified.

Stability

The long-term and accelerated stability of the drug product have been assessed, including stability under thermal cycling (stress) conditions and photostability.

The stability data provided support the proposed shelf-life for the drug product of 24 months from the date of compounding, stored at the intended storage condition of + 5 ±3°C in the primary container closure system (protected from light).

Bioavailability

Two bioavailability studies were included in the submission. As is typical for monoclonal antibodies, these were parallel group studies. The enzyme-linked immunosorbant assay (ELISA) test method used to determine the levels of certolizumab pegol in the subjects' plasma samples was suitable with a range of 4 to 333 ng/mL and by dilution of the samples this range could be extended to 3,330 [redacted]

Study CDP870-038

This study compared the injection solution proposed for supply in Australia with the powder for injection used in the Phase III clinical studies. Forty eight (48) subjects (24 in each arm) received a 400 mg dose of one of the products by subcutaneous (SC) injection. The results do not indicate bioequivalence of the two treatments using the usual criterion that the 90% confidence intervals of Cmax and AUC must fall between 80% and 125% with the results for the proposed injection solution being lower than those for the powder for injection used in the clinical studies. This was brought to the attention of the Delegate for consideration. In relation to this it was noted that:

- Although there was a large inter-subject variability, there was no statistically significantly difference between the results for the two products.
- The two products had significantly different assays and that if dose normalization was performed the lower limit for AUC increased to 78% and the lower limit for Cmax increased to 80%.
- Due to the nature of the powder for injection where each vial contained 280 mg of drug substance, it is conceivable that the dose administered from this product was greater than 400 mg.
- As a result it would not be unreasonable to accept that the two products used in this study are essentially bioequivalent.

Study CDP870-003

This study used a 20 mg/mL intravenous (IV) injection solution administered at a dose of 1 mg/kg and a 200 mg/mL SC injection solution administered at doses of 20 mg, 60 mg and 200 mg. The SC injection solution was not the formulation proposed for supply in Australia. Only 6 subjects were used in each group, and this study was only evaluated in relation to absolute bioavailability (and not in relation to whether the dose-response was linear or not). The results indicated that the absolute bioequivalence of the SC injection was ~80% with a range of 76-88. This study has also been reviewed by the clinical evaluator.

If there are no clinical objections to the two issues highlighted above, approval of this submission can be recommended with respect to the biopharmaceutical data provided for review.

Quality summary and conclusions

Generally, all aspects of chemical, pharmaceutical and biological documentation have been reviewed and found to comply with the current guidelines.

Generation, characterisation and stability of the cell substrate have been described in detail. Cell banks have been established and appropriately maintained with procedures in place for renewal of the cell banks to ensure continued supply of the product.

The drug substance manufacturing process has been shown to be consistent and capable of producing a high quality product. In-process controls have been defined to ensure consistency and quality.

The drug substance have been extensively characterised to define its physicochemical and biological characteristics.

Impurities arising from the manufacturing process have been identified and shown to be adequately controlled or removed.

The drug product manufacturing process and in-process controls are described in detail and are adequate.

The release specifications for the drug substance and drug product and shelf-life specifications have been revised and tightened to enhance product quality.

Stability data support the proposed shelf-life of the drug product of 24 months stored at 2° to 8°C.

Pathogen safety in term of safety from viral, TSE and other adventitious agents have been assessed as acceptable.

Approval of this submission can be recommended with respect to the biopharmaceutical data provided there are no clinical objections to the lack of bioequivalence.

As with all new biological entities, batch release testing of the first five batches by the TGA's Office of Laboratories and Scientific Servicers (OLSS) is recommended to verify quality and consistency of manufacture. Subject to the Delegate's agreement, batch release conditions should be added to the conditions of registration of this product.

III. Nonclinical findings

Introduction

The non-clinical dossier included primary pharmacodynamic, secondary pharmacodynamic, safety pharmacology, pharmacokinetic and toxicology studies. All pivotal safety studies were good laboratory practice (GLP) compliant. Use of certolizumab pegol in combination with methotrexate was not investigated in the non-clinical dossier. Some pharmacodynamic and pharmacokinetic studies compared certolizumab pegol with other currently registered anti-TNFα agents. Overall, the non-clinical dossier was adequate for a recombinant product that is a new chemical entity.

The second word, pegol, in the name of the substance indicates that the monoclonal antibody has been PEGylated. This word will be omitted from the remaining sections of this document for simplicity.

Pharmacology

Primary pharmacodynamics

A summary of the comparative binding characteristics of certolizumab for human and cynomolgus monkey soluble and mTNF is shown in Table 1.

Table 1: Summary of certolizumab binding and neutralization characteristics on Human and Cynomolgus Monkey soluble and membrane TNFα.

	Human TNFα	Cynomolgus Monkey TNFα
Binding affinity (soluble TNFα)	90 pM	3590 pM
Neutralization IC_{90} using L929 murine cells (soluble TNFα)	0.004 µg/mL	10 µg/mL
Saturation of membrane TNFα on lymphocytes, monocytes, neutrophils	10 µg/mL	10 µg/mL

The *in vitro* binding affinity of certolizumab to soluble rhuTNFα (23.5 pM; 86-92 pM) was considerably higher than that to recombinant rhesus (1590-fold) and recombinant cynomolgus monkey TNFα (40-fold; 3196-fold).

In *in vitro* L929 cytotoxicity assays, certolizumab selectively neutralised soluble human TNFα with an IC90 of 1-4 ng/mL. No cross-reactivity was observed between certolizumab and native TNFα produced in rat, guinea pig and rabbit and only weak cross-reactivity was seen with dog (IC90 not achieved). In addition, no reactivity was detected between certolizumab and recombinant mouse and rat TNFα. Although certolizumab was shown to be able to neutralise native non-human primate TNFα, it had a 950 to 3000-fold reduction in potency when compared to human TNFα. Moreover, certolizumab was effective at inhibiting rhuTNFα binding to human p55 and p75 TNF receptors and did not bind to lymphotoxin at concentrations up to 1 mg/mL. Certolizumab was also able to bind and neutralise human membrane TNFα.

In vitro studies were performed to compare certolizumab with other available anti-TNF antibodies. Surface plasmon resonance analysis (BIAcore) of soluble TNFα showed certolizumab to have a 2 to 3-fold higher binding affinity than infliximab and adalimumab. Neutralizing potency was also 3-fold greater. In other mechanistically oriented studies, pre-incubation of primary human monocytes or a human monocyte-like cell line with certolizumab, infliximab or adalimumab resulted in inhibition of cytokine release (TNFα and IL-1β) in response to LPS challenge.

Saturation binding and competition assays confirmed that certolizumab could also bind to and saturate mTNFα of cynomolgus monkey. Interestingly, unlike the case of soluble TNFα discussed above, saturation of mTNFα of cynomolgus monkey and human monocytes, lymphocytes and granulocytes appeared to be achieved at the same concentration of 10 µg/mL certolizumab.

Because certolizumab does not recognize TNFα from species other than primates, *in vivo* efficacy was evaluated using various animal models of inflammation in which human TNFα is the physiologically active molecule. Certolizumab dose-dependently inhibited rhuTNFα-induced peritoneal neutrophil infiltration in mice (intraperitoneal (IP) effective dose in 50% (ED50) of 0.052 mg/kg), rhuTNFα-induced pyrexia in rabbits (intravenous

(IV) ED50 of 0.003 mg/kg), and prevented disease development in a transgenic rhuTNFα mouse model of arthritis (10-30 mg/kg IP, twice weekly for 9 weeks).

Overall, the *in vitro* primary pharmacodynamic studies confirmed that certolizumab binds TNFα from humans (with high affinity) and non-human primates (with somewhat less affinity) but had little or no affinity for TNFα from standard lab species such as rat, dog, guinea pig and rabbit. Other studies showed that certolizumab is able to reduce inflammation caused by TNFα *in vivo*, and therefore demonstrated the potential for efficacy of certolizumab in TNFα-associated disease processes such as rheumatoid arthritis.

Secondary pharmacodynamics and safety pharmacology

To determine whether the unique structure of certolizumab affects the mechanism of action, comparative studies were undertaken to assess potential differences/similarities between certolizumab and three currently marketed anti-TNFα therapies: infliximab, adalimumab, and etanercept. Certolizumab was unique in that it did not mediate complement-dependent or antibody-dependent cell-mediated toxicity, or induce cell apoptosis at concentrations up to 100 µg/mL.

Certolizumab did not show any unexpected binding at 3 µg/mL (optimal staining on positive control tissue) or 10 µg/mL (mean trough plasma concentration in patients dosed at 400 mg per month) in a standard in vitro human tissue cross reactivity study. A cynomolgus monkey cross reactivity study was not performed.

No traditional safety pharmacology studies were performed. This is acceptable given that:

- previous experience with other TNF-α blockers (for example, European Public Assessment Reports for infliximab, adalimumab and etanercept) suggests that neutralization of TNFα does not appear to have adverse effects on the major vital systems (central nervous system (CNS), cardiovascular, respiratory) in either humans or animals;
- there was no cross-reactivity of certolizumab with the standard panel of human tissues, and
- there were no adverse effects on the central nervous, respiratory or cardiovascular system observed in a combined 13/26-week study in the cynomolgus monkey, at dose levels resulting in Cmax more than 70-fold higher than anticipated in patients at the maximum recommended human dose (MRHD).

Pharmacokinetics

The quantitative accuracy of the ELISAs used to detect certolizumab and anti-certolizumab antibodies was limited by certolizumab interference with the antibody analysis, and vice versa. A nuclear magnetic resonance (NMR) assay was used to analyse the pharmacokinetics of PEG-containing substances in blood and urine.

Dose proportional exposure of certolizumab (based on the maximal plasma concentration (Cmax) and area under the curve (AUC)) values was observed in cynomolgus monkeys following single or repeat dose administration by either the subcutaneous (SC) or IV route. While bioavailability after SC dosing was not formally studied in cynomolgus monkeys, if linearity is assumed between dose and plasma concentration then a comparison of AUC values from single dose studies (for example 50 mg/kg IV & 31 mg/kg SC) suggests that bioavailability is essentially complete by the SC route in this species.

PEGylation of the Fab' fragment resulted in a prolonged absorption phase after SC dosing (time to maximal plasma concentration (Tmax) of 2-3 days in monkeys and 1-2 days in

rats). Certolizumab was eliminated from the plasma of cynomolgus monkeys in a biexponential manner following IV dosing, with distribution and elimination half-lives of approximately 12 hours and 8 days, respectively. This suggests that certolizumab should have been cleared by the body after approximately two months, consistent with observations from recovery animals of the combined 13/26 week and 52-week monkey studies where no certolizumab was detected in the plasma of high dose animals 12- 16 weeks after the last dose. The PEG moiety has a longer retention time in the body as indicated by the histopathology data in the high dose recovery animals of the combined13/26-week and 52 week studies. In some animals the presence of anti-certolizumab antibodies resulted in shortened t1/2 values for certolizumab.

Tissue distribution of certolizumab in rats showed highest concentrations in blood, kidney and lung with no tissue accumulation or uptake of the PEGylated fragment. Certolizumab and immunoglobulin G (IgG) shared similar clearance and tissue distribution profiles, which were very different to those of Fab' fragment. Tissue distribution studies using NMR detection of PEG indicated a proportion of the PEG was distributed to tissues such as liver and spleen, from where it was cleared with a half-life of about 20 days, much longer than the half-lives of intact certolizumab and cTN3 PF (about 2 days). Such a time course is consistent with the proposition (Lamka et al., 1995) that the administered PEG is cleared from the circulation by macrophage uptake within the lymphoreticular system.

No studies have been conducted to examine the excretion of the protein component of certolizumab as it is expected to undergo proteolysis and excretion via urine. Cumulative urinary excretion of PEG-derived material in rats following a single dose of 400 mg/kg of certolizumab was 63% of the given dose after 12 weeks with an additional 18% in the faeces. Urinary PEG-derived material was shown to be 40 kDa PEG.

Drug interactions

No specific pharmacokinetic drug interaction studies have been conducted.

Relative exposure

No repeat dose human pharmacokinetics have been provided in the current submission. The relative exposure multiples for Cmax and area under the curve from time zero to infinity ($AUC_{0-\infty}$) attained in the pivotal cynomolgus monkey SC studies are summarized below. Comparisons are made against the equivalent parameters measured for humans at the Maximum Recommended Human Dose (MRHD) of 400 mg.

Given that very few animals had detectable antibodies during the dosing period the results in Table 2 suggest that cynomolgus monkeys were exposed to high Cmax and AUC multiples relative to that anticipated at the MRHD, particularly in the pivotal repeat dose studies.

Toxicology

Certolizumab binds to human TNFα with high affinity and cross reacts with TNFα from non-human primates. Thus, the cynomolgus monkey was selected as the main species for safety testing which include one single dose IV study, two repeat dose studies (4 week IV and 13/26 week SC) and one immunotoxicity 52 week SC study. Group sizes and maximum study durations were adequate. The dosing regimens for the repeated dose studies were designed to mimic anticipated dosing regimens and dose route in the clinic. Plasma concentrations of certolizumab in all studies were maintained at levels well in excess of the neutralising potency for cynomolgus monkey TNFα (IC90 10 µg/mL).

Single dose toxicity

In cynomolgus monkeys, certolizumab at a single dose up to 400 mg/kg IV was well tolerated and showed no evidence of acute or delayed toxicity over a 28 day observation period. In a single IV dose range-finding study in rats, certolizumab was well tolerated without any adverse findings and the No Observable Effect Level (NOEL) was determined to be >1000 mg/kg. Certolizumab was also well tolerated after single dose IV administration in rats and cynomolgus monkeys with a NOEL of > 1000 mg/kg in the rat and good tolerability at 400 mg/kg (the highest dose tested) in the monkey.

Table 2: Relative exposure multiples attained in pivotal cynomolgus monkey toxicity studies

Species	Study report Study details	Dose (mg/kg)	$AUC_{0-\infty}$ (mg.h/mL)	Relative AUC	C_{max} (µg/mL)	Relative C_{max}
cynomolgus monkey	40000998 40001080 Single dose, SC	3	12	0.4	36	1.2
		31	112	3.3	480	15
	40001393 Single dose, SC	10	45	1.3	114	3.7
	40001074[4] & 40001020[4] Once weekly 4 weeks IV	50	696	20	N/A	N/A
	40001545 40001077 40001586 Once weekly 13 or 26 weeks SC	10 (26 weeks)	609[4]	18	248	8
		100 (13 weeks)[1]	2690	79	2600	84
		100 (26 weeks)[1]	5151	152	2196	71
	40001535[2] Once weekly 52 weeks SC	50	5030	148	930	30
		100	8216	242	1716	55
Human[3]	certolizumab-003 Single dose SC	2.86	34	N/A	31	N/A

[1]Following the dosing, animals also had a 13 week treatment-free period; [2]AUC calculated from mg.day/mL (values from the study report, and are multiplied by 24); [3]2.86 mg/kg is equivalent to 200 mg/dose, assuming a body weight of 70 kg. The reported AUC value of 16.8 mg.h/mL was multiplied by 2 to get the value at MRHD; N/A: Not Applicable

Repeat dose toxicity

General

Across the repeat doses studies a number of haematological and clinical chemistry parameters (including reductions in alkaline phosphatase (ALP), total protein, and cholesterol) were found to be significantly different compared with controls. These changes were not consistent and lacked dose proportionality, had high intra-group variation, or had values still within pre-treatment or historical background ranges. At the end of the recovery period, all of these parameters resolved to control levels and were not associated with any histological changes, suggesting they are unlikely to have relevance in clinical practice.

Haematological effects

The two main haematological effects noted in the repeat dose monkey studies were:

- A decrease in platelets, red blood cells and white blood cells
- An increase in some coagulation parameters (activated partial thromboplastin time (APTT) and prothrombin time (PT))

Dose-related decreases in haemoglobin (Hb), red blood cells (RBC) and packed cell volume (PCV) were noted immediately after infusion in all groups including controls in the 28 day IV study. This reduction cannot be solely attributed to an increased circulatory volume as the recovery at 24 hours after infusion on each occasion was only to levels which were slightly less than those observed prior to infusion. In contrast to the RBC, the total white cell count (immediately following and 24 hours after infusion) did not show dose-related variability and had no consistent pattern of increase or decrease in all groups. All of these altered haematology parameters resolved to the pre-treatment values during the treatment-free period. In the 52 week SC study a similar but less pronounced effect was also seen, for example, up to 10% decrease in Hb, RBC and haematocrit levels for males in both treated groups compared with controls throughout the treatment period. These changes were reversible and were not accompanied by any adverse effects on the monkies' health. None of these effects were noted in the combined 13/26-week SC study, suggesting that these effects are variable in this species.

Dose-related increases in PT (≤ 18%) and APTT (≤ 39%) were observed in the 28 day IV study. At Day 39 and 55 during the treatment-free period, PT was comparable in all animals and similar to pre-treatment values, while at the end of the treatment-free period, APTT was still elevated in all treated groups (max + 81% in the 400 mg/kg group). In the 52 week SC study, statistically significant increases (up to 30%) in APTT times were seen in all certolizumab treated animals during Week 12, 24, 41 and 52 compared with control groups. However, the extent of the changes was small when compared to Inveresk historical background range and the PT remained unaffected. The changes in both studies were not accompanied by evidence of any increased bleeding times following blood sampling procedures or bleeding-related events in-life or from histopathology. Furthermore, no changes in APTT were seen in monkeys dosed with up to 100 mg/kg weekly in the combined 13/26 week SC study. Increases in APTT were observed in some but not all clinical trials: "occasional weak but inconsistent signals of increased clotting time and bleeding with certolizumab in both CD and RA patient populations" according to the Clinical Expert Report.

Overall, the mechanism underlying the increases in coagulation parameters is not fully understood, especially in the absence of abnormal bleeding-related events. No such changes have been reported either non-clinically or clinically with other TNFα inhibitors, suggesting that TNFα neutralisation is unlikely to be the cause. Particular caution should be taken to interpret these analytical results, as an in vitro investigation has suggested that the PEG moiety of certolizumab may interfere with some phospholipid reagents used

in the assay, raising the possibility that different methods may have the potential to influence the assay results. The sponsor's findings are supported by published studies which have shown that PEGs and different PEG surfaces can cause a prolonged clotting time (Cheng et al., 2003; Hansson et al., 2005).

Vacuolation

The common microscopic observation following repeat dosing in all three cynomolgus monkey pivotal safety studies was the vacuolation of cells, mainly in histiocyte/macrophages in the haemolymphoreticular system. The incidence of vacuolation (foamy macrophages) showed a dose and duration of treatment relationship. Following treatment-free periods, there was clear evidence of resolution as shown by diminution of the numbers and extent of vacuolated macrophages and epithelial cells. No evidence of altered cell morphology, necrosis or inflammation was found to be associated with the observed macrophage or epithelial cell vacuolation and no adverse effects on immune competence was noted, even after extended duration, high exposure to certolizumab (52 week SC study).

In the 13/26-week toxicity study there was no evidence of tissue vacuolation and only minimal vacuolation at the injection sites at the lowest dose level (10 mg/kg), with no clear inflammatory response noted. The relative exposure to certolizumab at this tissue vacuolation NOEL (based on AUC) is 18-fold higher than in patients on the MRHD of 400 mg.

The observed histiocytic vacuolation is likely a result of uptake of the normal physiological processing of the PEG moiety by macrophages and other phagocytic cells, as has been observed previously (Conover et al., 1996a; Conover et al., 1996b; Working et al., 1998). Similar findings have been observed with other PEGs (Working et al., 1998). Despite such findings, in vitro studies on human macrophages demonstrated that they retained functions such as cytokine production, antigen presentation and phagocytosis, even at high in vitro exposure levels that are known to cause vacuolation.

Overall, the observed vacuolation in monkey repeat dose at high certolizumab exposure levels is not of clinical concern.

Rat studies

Interestingly, the two 5-day repeat-dose studies in rats conducted with certolizumab (IV once daily at doses up to 400 mg/kg) revealed similar findings to the monkey studies: small reductions in haematology variables, increases in PT and APTT, and histiocyte vacuolation. As certolizumab has minimal affinity for rat TNFα these findings suggest that these toxicities are not attributable to TNFα binding.

Antibodies to certolizumab were detected in 2/22 animals following single dose and 21/116 animals following repeat dose administration in cynomolgus monkeys, without any clear dose-response relationship. Only 3/23 anti-certolizumab positive animals exhibited altered certolizumab pharmacokinetic profiles: (i) 1 female at 50 mg/kg had increased clearance rate in the 28 day study; and (ii) 2 females at 10 mg/kg had increased clearance from 9th dose in the 13/26 week study. In addition, an increased certolizumab clearance has also been noted in 1 male at 50 mg/kg in the 52 week study but this animal had no detectable anti-certolizumab antibodies. All the examined antibodies are of immunoglobulin M (IgM) class at earlier time points (single dose study) and switched to IgG at later time (1 and 2 months). They are directed against the idiotype of certolizumab and not any other epitopes on certolizumab. No antibodies against PEG have been detected.

While there was a 38% decrease in T lymphocytes noted in males receiving 100 mg/kg for 13 weeks, the values were within the historical background range. This finding is also unlikely to be clinically relevant given the high exposure (about 80-fold based on AUC) to

certolizumab and the fact there were no infections and no difference in the KLH tests at the end of the treatment periods (up to 26 weeks). This is consistent with the clinical data which has shown only a low incidence of mild injection site reactions that are unrelated to dose.

Changes in the counts of the investigated immunological marker sets (e.g., CD4, CD8, CD40, B cells) were noted over time in the 52 week SC study during both the treatment and recovery periods. However, these changes affected both treated and untreated groups suggesting that the observations are not treatment-related.

Genotoxicity

Genotoxicity tests are considered to be of limited value for a recombinant product like certolizumab (ICH S6 "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals). Nevertheless, a standard in vitro/in vivo package of genotoxicity was conducted in order to investigate the safety of the linker-PEG construct:

- Certolizumab showed no mutagenic activity was seen in an appropriately conducted Ames test at up to 4997 μg/plate
- Certolizumab was not clastogenic in an appropriately conducted in vitro cytogenetics assay using human lymphocyte cultures
- Certolizumab was negative in the in vivo mouse micronucleus test following two consecutive daily doses of up to 416 mg/kg. Although no exposure determinations were performed, a similar dose regime (up to 400 mg/kg IV for 5 days) in rats showed plasma concentrations of about 6 mg/mL (>170 times the human mean certolizumab plasma concentration at the MRHD) at 24 hours after the last dose.

Negative genotoxicity results have also been reported with other TNFα inhibitors (EPAR etanercept and EPAR infliximab) and other PEGs (Working et al., 1998).

Carcinogenicity

Like other approved anti-TNFα products, no conventional rodent carcinogenicity studies were carried out with certolizumab, in line with ICH guideline S6 and consistent with the lack of certolizumab binding to rat and mouse TNFα. Nevertheless, the 52 week monkey study revealed no lymphomas and no treatment-related effects on lymphocyte subset numbers. Examination of selected haemolymphoreticular-associated tissues did not reveal any proliferative changes suggestive of any neoplastic process. Moreover, the combined 13/26 monkey study also showed no haematological or pathological changes suggestive of any pre-neoplasia.

Reproductive toxicity

Certolizumab does not recognize TNFα from commonly used rodents for reproduction studies. Therefore, the reproductive toxicity of certolizumab was assessed using a homologous agent, an anti-murine TNFα PEGylated Fab', termed cTN3 PF, with a similar structure to certolizumab. Homology of cTN3 PF to certolizumab is based on certolizumab being a fully humanized Fab' fragment against human TNFα, conjugated to 40 kDa PEG. Chimeric TN3 PF has an affinity for rat TNFα of about 6.7 nM, and like certolizumab has a half-life ($t_{1/2}$) of about 2 days and a lack of an Fc region (which makes it unlikely to cross the placenta).

Studies on fertility and early embryonic development, embryotoxicity and pre/post-natal development including maternal function, were performed at doses up to 100 mg/kg IV twice weekly in rats. The mean plasma levels of cTN3 PF obtained at the high dose of 100 mg/kg in these studies exceeded the IC90 for rat TNFα by 75 to 2190-fold.

In females, no effects on fertility or reproductive performance were noted following twice weekly IV administration of cTN3 PF at dose levels up to 100 mg/kg for 2 weeks prior to mating, during mating with untreated males and on Days 1 and 4 of gestation.

No treatment-related findings of concern were observed in males treated with cTN3 PF for 4 weeks prior to mating, throughout a 2-week mating period (with untreated females) and for 4-weeks after completion of the mating period. A slight increase in testes weight was not associated with any histological findings and the reduced sperm motility noted was only seen at the highest dose of 100 mg/kg, with only one animal showing values outside concurrent and historical control values. Mean sperm counts also tended to be slightly lower in both treated groups compared with controls but attained no statistical significance. Overall, these results raise no clinical concerns for human fertility and general reproductive performance given the marginal nature of these effects in males and the very high exposure to cTN3 PF.

In the rat embryofetal development study cTN3 PF was administered IV at dose levels of 20 or 100 mg/kg on 2 (GD1 and GD4) or 4 (G6, G9, G13 and G16) occasions during gestation, including the period of organogenesis. While the top dose (100 mg/mL) was the maximum dose tested, no signs of maternal toxicity were noted. Neither the incidence nor types of malformations detected showed any pattern suggestive of a treatment-related effect. There was a finding of malformed kidneys in four foetuses in the 20 mg/kg dose groups; three from one dam. However, the absence of a similar finding in the 100 mg/kg dose groups suggests no association with treatment. The NOEL for maternal toxicity and embryo-foetal development was 100 mg/kg.

When cTN3 PF was administered IV to rats at 30 or 100 mg/kg during gestation and lactation there were no treatment related effects on the parent animals and no adverse effects on embryofetal survival or on subsequent survival, growth, physical or functional development of the lactating pups through to weaning or post-weaning development. There was only a limited transfer of cTN3 PF to dam milk with a milk:plasma ratio of approximately 10% measured on day 22 (lactation day 2, consistent with previous observations) and only limited transfer to foetal plasma via the placenta (less than 0.3% of maternal levels on GD20) or pup plasma via milk (milk:plasma ratio of approximately 10% measured on lactation day 1). The No Observable Adverse Effect Level (NOAEL) was 100 mg/kg cTN3 PF.

Overall, no adverse effects were seen in any of the reproductive studies following sustained TNFα suppression with cTN3 PF. In addition a similar reproductive toxicity program was completed using a PEGylated whole antibody (designated cTN3γ1) of comparable potency against TNF, which showed substantial placental transfer to the foetus, milk transfer exposure and this was also devoid of reproductive and developmental effects.

Local tolerance

Three local tolerance studies were conducted in rats. At a single dose of 800 mg/kg SC, only minor subcutaneous oedema at the injection site was observed, which resolved by Day 29. Histological changes at the injection sites characterised by lymphohistiocytic infiltrates, oedema, myodegeneration, vacuolated macrophages, necrosis and fibrosis were observed following the administration of both liquid and lyophilised formulations of 200 mg/kg. There were no remarkable differences in the level of severity of histological changes between the two formulations. The local tolerance to certolizumab was further supported by toxicity studies in cynomolgus monkeys where only minimal vacuolation was seen with no clear inflammatory response (26 week, 10 mg/kg/injection, 1.8-fold the MRHD based on mg/kg) or minimal to mild inflammation and vacuolated macrophages (52 weeks, 100 mg/kg, 18-fold the MRHD based on mg/kg). Furthermore, the Clinical

Expert Report noted that "the incidence of injection site AEs with certolizumab has been generally low, no different from placebo, mild in severity and unrelated to dose".

The toxicology studies were conducted with batches of certolizumab manufactured by Processes 1, 3, 4, 6, 7 and 9. In addition, in vitro and in vivo comparisons were made between certolizumab manufactured by Processes 3, 6 and 7 and these studies did not show any significant differences in the in vitro functionality or higher order structure or in vivo potency of these materials. The changes in manufacturing processes did not result in any changes to certolizumab that would invalidate the results obtained from the pivotal toxicology studies of certolizumab in assessing the safety for humans.

Paediatric use

There were no non-clinical studies in young animals to support the use in children.

Nonclinical summary and conclusions

Non-clinical pharmacological studies conducted in vitro demonstrated that certolizumab binds to TNFα from humans with high affinity. Furthermore, certolizumab was able to reduce inflammation caused by TNFα in humanised animal models *in vivo*, and therefore demonstrated the potential for efficacy in TNFα-associated disease processes such as rheumatoid arthritis.

Non-clinical toxicological studies performed with certolizumab up to high exposure margins revealed no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

While there were no studies on the carcinogenic potential of certolizumab there was no evidence of proliferative changes or effects on lymphoid tissue or lymphocyte subset counts in studies up to 52 weeks duration in a relevant animal model (cynomolgus monkey).

Reproductive toxicity studies performed in the rat with a rodent, PEGylated anti-murine TNFα Fab' fragment revealed no adverse effects at IV doses up to 100 mg/kg suggesting that neither administration of high doses of a PEGylated Fab' nor TNFα inhibition adversely affects male and female fertility, embryo-foetal development, parturition or post-natal development.

The safety of the combined use of certolizumab and methotrexate was not investigated in the non-clinical dossier and will depend on the clinical trial data.

Overall, the toxicology studies conducted with certolizumab did not reveal any safety issues of clinical concern. Therefore, there are no objections to the registration of Cimzia for the proposed indication.

IV. Clinical findings

Introduction

In general, the submission was well written and clearly presented. The trials were conducted according to Good Clinical Practice guidelines and in compliance with the principles of the Declaration of Helsinki.

The RA clinical trial program evaluating the safety and efficacy of certolizumab includes 6 controlled and 4 open-label (3 of which are on-going) studies conducted in approximately 30 countries predominately involving the USA, Western and Eastern Europe, Central and

South American, and Scandinavia. In the blinded clinical studies, a total of 1510 subjects with RA received at least 1 injection of certolizumab in various dosing regimens – 639 patients received 200 mg every 2 weeks (q2w), 636 patients received 400 mg q2w, and 235 patients received 400 mg every 4 weeks (q4w). When the patients subsequently exposed to certolizumab in the open label extension studies are added to the controlled studies, total patient exposure to certolizumab exceeds 2300 individuals. In the pooled clinical safety database (up to 31/8/2007), the total duration of exposure is greater than 4000 patient-years with over 800 subjects receiving drug for at least 24 months. The median duration of drug exposure is 1.7 years per subject and approximately 76% of all certolizumab-treated subjects have received the drug for > 12 months. The optimized liquid formulation of certolizumab is the proposed commercial formulation and the current dataset contains 201.5 patient-years of exposure to this particular formulation, compared with a greater than 3-fold (702 patient-years) exposure to the lyophilized formulation. The minimum criterion in the relevant EU guideline for drug exposure in adult patients with RA is 100 patient-years. Four randomized, placebo-controlled, double-blind studies in patients 18 years of age or older with active RA (at least 9 swollen and tender joints at baseline) of at least 6 months duration have been conducted, and 2 of these studies can be considered pivotal - Study CDP870-027 (also titled the RAPID 1 Study) and Study CDP870-050 (also known as the RAPID 2 Study).

Pharmacokinetics

The submission contained a large quantity of data in relation to the pharmacokinetics of certolizumab:

- 3 healthy volunteer pharmacokinetic (PK) studies - CDP870-001 (Intravenous formulation), CDP870-003 (SC and IV formulations) and PHA-024 (SC formulation only),
- 2 bioavailability studies (CDP870-003 and CDP870-038),
- 2 dose finding phase II studies (CDP870-002 and CDP870-004),
- 1 open-label PK interaction study with MTX (Study PHA-001),
- Various PK analyses of patient subgroups within the 4 phase III clinical studies (CDP870-011, -014, -027 and -050), and
- 5 Population PK reports (of particular relevance is Study C87068 which is a population PK (POPPK) analysis in RA subjects using pooled data from 6 studies – PHA-001, and CDP870-004, -011, -014, -027 and -050).

Absorption, distribution, metabolism, excretion

The clinical pharmacology of certolizumab in patients with RA and healthy volunteers has been characterized from the analysis of data from approximately 2000 subjects in several studies including dose finding studies, pharmacokinetic trials and population pharmacokinetic and/or pharmacodynamic analyses. The main results can be summarized as:-

- Compared to IV dosing, SC dosing of certolizumab has an absolute bioavailability of ~80%.
- Certolizumab has a high affinity for human TNF but does not neutralize lymphotoxin.
- The major route of elimination for the de-conjugated polyethylene glycol component is renal excretion (which may have unstudied clinical implications).

- Certolizumab demonstrates linear dose-related concentrations across the dose range tested and has a mean terminal half-life of approximately 14 days.
- Population pharmacokinetic analysis demonstrates moderate inter-individual (~30%) and inter-occasion variability (~22%) in certolizumab,

Bioequivalence

The proposed commercial formulation (optimized liquid) of certolizumab has similar pharmacokinetic properties to the more commonly used formulation (lyophilized) in the clinical trials, but there are some potentially significant differences such as an approximately 10% lower AUC and Cmax, and a slightly higher incidence of anti-certolizumab antibody formation in the single short-term follow-up study examining these differences.

Dose response

Studies of certolizumab in subjects with RA have included a variety of doses (50, 100, 200, 400, 600 and 800 mg) and dosing regimens (once every 2 weeks [q2w] and once every 4 weeks [q4w]).

Study CDP870-002 was the initial dose-finding study in subjects with active RA. It was conducted as a double-blind, placebo-controlled, ascending dosage group (1, 5, 20 mg/kg) trial in 4 centres in the UK using the initial liquid formulation of certolizumab. Plasma levels of certolizumab were maximal at the end of infusion for both treatment periods (27.8, 109.3 and 467.7 mcg/mL for the 1, 5 and 20 mg/kg dose groups, respectively) and declined slowly over the 8 week follow-up period. For the first treatment period, certolizumab was detectable in the plasma at 8 weeks in 7of 8 patients receiving 5mg/kg and all patients receiving 20 mg/kg. For the 1 mg/kg dose group, certolizumab was not detectable at approximately 6 weeks post-infusion. The AUC values reflected dose proportionality and the PK profiles seen in this study were comparable to those observed in healthy volunteers. The elimination was calculated to be approximately 2 weeks and mean clearance profiles after the second infusion were similar to the first treatment phase.

The initial phase III clinical studies (CDP870-011 and CDP870-014) used a dosing regimen of 400 mg q4w. The results of this study demonstrated: (1) certolizumab at doses of <400 mg q4w had reduced (sub-optimal) comparative efficacy in treating the signs and symptoms of RA, (2) certolizumab 400 mg q4w was equally as efficacious as 600 mg q4w, and (3) certolizumab 800 mg q4w achieved responses that were numerically higher for the individual American College of Rheumatology (ACR) disease activity measures compared to 400 mg q4w but that this incremental response was not meaningful.

The sponsor decided to reduce the dosing frequency from q4w to q2w for 2 principal reasons. Firstly, it theorized that q2w dosing would reduce the peak to trough plasma concentration ratio of certolizumab during the dose interval and potentially improve clinical response rates. This theory was supported by a PK modelling analysis. Secondly, the sponsor wished to align its dosing schedule to that of other marketed anti-TNF drugs. Hence, the 2 latest and pivotal phase III studies (CDP870-027 and CDP870-050) used CDP870 200 mg and 400 mg q2w dosing regimens. Furthermore, predictions based on the PK/PD modelling (Study C87079) indicated that a loading period is important in achieving steady state drug levels more rapidly and therefore a more rapid onset of response that is comparable to that seen in the 400 mg dose group. As such, the pivotal CDP870-027 and CDP870-050 Studies included a dose of 400 mg q2w for the initial 3 doses.

Special populations

Ethnicity

The effect of ethnicity on the PK of certolizumab was investigated in Study PHA-024 where healthy Japanese and Caucasian subjects received single SC doses of 100, 400 and 800 mg of certolizumab. The PK profile was similar in both ethnic groups at all tested doses.

Age, gender, race, minor renal impairment

Two POPPK analyses (CDP870-039 and C87068) did not reveal any clinically significant changes in the PK of certolizumab or its PEG fraction as result of age, gender, race or mild renal impairment. In particular, 78 patients (approximately 13% of the total cohort evaluated) with RA were > 65 years of age in the POPPK report C87068.

Moderate/severe renal impairment

As a note of caution there is insufficient data to provide a dosing recommendation in subjects with moderate or severe renal impairment, but it is expected that the elimination of the PEG fraction is dependent on adequate renal function.

Hepatic impairment

Specific clinical studies have not been performed to assess the effect of hepatic impairment on the PK of certolizumab.

Children

Specific clinical studies have not been performed in children (that is <18 years of age).

Extremes of body weight

The POPPK Study C87068 also indicated that extremes of body weight were predicted to have an effect compared with a 70 kg reference patient of approximately +30% for a 40kg subject and -30% for a 120 kg subject on certolizumab clearance.

Drug Interactions

Methotrexate, corticosteroids and purine analogues have no effect on the pharmacokinetics of certolizumab and vice versa.

Pharmacodynamics

Pharmacodynamic Effects

The majority of the pharmacodynamic (PD) information pertaining to certolizumab was derived from pre-clinical studies, however, this submission did contain a pharmacokinetic (PK)/PD analysis (C87079) which used data from 5 clinical studies (CDP870-004, -011, -014, -027 and -050) to investigate the exposure-response relationship for the primary efficacy endpoint of ACR 20 response in patients with RA.[1]

The analysis revealed that the average plasma concentration of certolizumab (regardless of the dose interval, that is 2 or 4 weeks) at the time of the ACR assessment best correlated in the PK/PD model, and that the use of MTX was a non-significant covariate.

[1] ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

The other significant findings from this analysis are:-

- The average plasma concentration of certolizumab during the dosing interval was similar for both the 200 mg q2w and 400 mg q4w dose regimens, and the PK/PD model predicted similar ACR response rate probabilities for the q2w (71%) and q4w (69%) dosing schedules.
- The main efficacy benefit of the loading regimen (400 mg at weeks 0, 2 and 4) is an improvement in the time to onset of ACR response. Predictions from the PK/PD model indicate an additional 9% probability of achieving an ACR 20 response rate at week 12 versus the non-loading regimen of 200 mg q2w. However, at week 22 the difference between the 2 loading regimens was reduced to a 3% improved probability of achieving an ACR 20 response.
- Simulations based on the exposure-response model predicted a similar (that is < 3% difference) probability of achieving an ACR 20 response at week 22 for the optimized liquid (proposed commercial formulation) versus the lyophilized formulation.

The formation of anti-certolizumab antibodies and neutralizing anti-certolizumab antibodies is another area of interest. The detection of antibodies is confounded by the known interference of certolizumab in the plasma with the anti-certolizumab antibody assay. The incidence of producing both types of antibodies to the drug is inversely proportional to the certolizumab dose in both healthy subjects and patients with RA.

In the 4 healthy volunteer studies where subjects received a single dose of certolizumab, 19% (24/126) developed anti-certolizumab antibodies. In the 4 placebo-controlled, phase III studies the overall incidence of anti-certolizumab antibody formation was 7.0% (105/1510). However, when certolizumab (across all dose regimens) was administered with concurrent MTX the incidence of antibody formation was 5.7% (80/1399), compared to when certolizumab was given as monotherapy (400 mg q4w) the incidence of anti-certolizumab antibody formation was 22.5% (25/111). The peak incidence for the formation of anti-certolizumab antibodies occurred relatively early in the treatment courses at 12-16 weeks after drug initiation. Of all the subjects who developed anti-certolizumab antibodies, approximately 30% (that is 2% overall) had neutralizing activity with further bioassay. The incidence and nature of anti-certolizumab antibodies was not different between the lyophilized or liquid formulations of the drug. The development of anti-certolizumab antibodies appears to have a moderate detrimental effect upon efficacy but no significant impact on the safety profile of certolizumab. In subjects who developed anti-certolizumab antibodies in the 2 pivotal studies (CDP870-027 and -050) receiving certolizumab 200 mg q2w, the ACR 20 response rate at week 24 was 44% (27 of 62) compared with 60% (342 of 572) in those individuals who remained antibody negative throughout the studies.

Efficacy

The data for the proposed indication in patients with RA is based on 2 pivotal phase III studies (Studies CDP870-027 and -050) which is supported by another 2 phase III studies (CDP870-011 and -014). The submission also included an interim report containing efficacy data from 1 of the 3 open-label extension studies (CDP870-015). This particular extension trial received patients who had previously been involved in Studies CDP870-011 and -014, and may be considered as supportive for the proposed indication listing. Trial summaries are shown in Table 3.

Table 3: Efficacy Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of treatment	Study Status; Type of Report
Efficacy and safety for RA	CDP870-027	Vol. 46 Sec. 5.3.5.1.4a Amdt in Vol. 69 Sec. 5.3.5.1.4b	**Primary:** To assess the efficacy of 2 dose regimens of CDP870 in combination with MTX vs MTX alone in: 1. the treatment of signs and symptoms in pts with active RA; 2. the prevention of structural damage in pts with RA. **Secondary:** To assess 2 dose regimens of CDP870 in combination with MTX vs MTX alone in: 1. safety and tolerability in pts with active RA. 2. improving physical function in pts with active RA. 3. achieving a major clinical response in pts with active RA. 4. Health Outcome Measures in pts with active RA. 5. assessing the PK profile and immunogenicity of 2 dose regimens of CDP870 with MTX.	Multi-centre, double blind, placebo-controlled, parallel group study.	Lyophilized; two sc injections every two weeks after randomization to one of the following treatment groups 1. Placebo: given as two injections of placebo at Baseline and then every two weeks. 2. CDP870 400 mg sc induction regimen at Baseline, Weeks 2 and 4, then CDP870 200 mg sc every two weeks. 3. CDP870 400 mg sc every two weeks: given as two injections of CDP870 at Baseline and then every two weeks.	982 (783 active, 199 placebo)	Rheumatoid arthritis patients on MTX	52 weeks	Full CSR reported Study complete RRCE06D1020 RXCE08B2030

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of treatment	Study Status; Type of Report
Efficacy and safety for RA	CDP870-050	Vol. 74 Sec. 5.3.5.1.5	**Primary:** To compare the efficacy of two dose regimens of liquid formulation CDP870 in combination with MTX to MTX alone in treating the signs and symptoms of pts with active RA. **Secondary:** To assess 2 dose regimens of certolizumab pegol in combination with MTX and MTX alone in: 1. the safety and tolerability of certolizumab pegol in pts with active RA. 2. The prevention of joint damage in pts with active RA. 3. Health Outcomes Measures in pts with active RA. 4. Improving physical function in pts with active RA. To characterize the PK profile and immunogenicity of 2 dose regimens of liquid certolizumab pegol in combination with MTX.	Multi–center, double–blind, randomized, placebo–controlled, parallel group study.	Liquid; CDP870 (induction of 400 mg sc for the first three dosing visits followed by 200 mg sc for the remaining dosing visits) CDP870 (400 mg sc) every two weeks Placebo	619 (492 active, 127 placebo)	Rheumatoid arthritis patients on MTX	24 weeks	Full CSR reported Study complete RRCE06D1018

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of treatment	Study Status; Type of Report
Efficacy & safety for RA	CDP870-011	Vol. 35 Sec. 5.3.5.1.2a Amdt in Vol. 39 Sec. 5.3.5.1.2b	**Primary:** To compare the efficacy of CDP870 400 mg every 4 weeks to placebo in treating the signs and symptoms of patients with RA who have previously failed at least one DMARD. **Secondary:** - To evaluate the safety and tolerability of CDP870 400 mg sc administered every 4 weeks - To characterize the effect of CDP870 on Health-related Outcomes - To determine systemic exposures and the immunogenic profile of CDP870	Double-blind, placebo-controlled, multi-center, parallel group comparison of the efficacy and safety	Lyophilized; CDP870 400 mg sc every 4 weeks Placebo every 4 weeks	CDP870: 111 Placebo: 109	Rheumatoid arthritis patients	24 weeks	Full CSR reported Study complete RRCE06C1440 RXCE07J1804

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of treatment	Study Status; Type of Report
Efficacy & safety for RA	CDP870-014	Vol. 40 Sec. 5.3.5.1.3a Safety summary Vol. 45 Sec. 5.3.5.1.3b	**Primary:** To compare the efficacy of CDP870 in combination with MTX to MTX alone in treating the signs and symptoms of patients with RA who are partial responders to MTX. **Secondary:** - To evaluate the safety and tolerability of CDP870 in combination with MTX - To characterize the effect of CDP870 in combination with MTX on Health Outcomes Measures - To characterize the immunogenic profile of CDP870 when it is used as combination therapy with MTX - To determine systemic exposures of CDP870	Double-blind, placebo-controlled, multi-center, parallel group comparison of the efficacy and safety of CDP870 in combination with MTX vs MTX alone.	Lyophilized; CDP870 400 mg sc every 4 weeks + MTX (10-25 mg/week). Placebo sc every 4 weeks + MTX (10-25 mg/week).	CDP870 plus MTX: 124 Placebo plus MTX: 119	Rheumatoid arthritis patients	24 weeks	Full CSR reported Study complete RRCE06C1441 RXCE05L2803

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of treatment	Study Status; Type of Report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies									
Safety and efficacy for RA	CDP870-015	Vol. 86 Sec. 5.3.5.2.1a Progress report Vol. 97 Sec. 5.3.5.2.1b	**Primary:** To assess the long-term safety and tolerability of CDP870 400 mg sc every 4 weeks in patients with RA from 011 & 014 studies. **Secondary:** - To assess the long-term efficacy of CDP870 400 mg sc every 4 weeks in the treatment of the signs and symptoms of RA. - To characterize the dose and type of additional arthritis medication(s) utilized by patients. - To assess the long-term impact of CDP870 on physical function.	Multi-center, open-label long-term safety study	Lyophilized; CDP870 400 mg sc every 4 weeks	402	Rheumatoid arthritis patients (some on MTX)	Ongoing	Study ongoing; Interim & progress report available RRCE06D1022 RRCE08C1906

There are 3 disease aspects to the proposed indication that need to be considered: firstly, to determine the adequacy of the data to support the claim of "reducing the signs and symptoms"; secondly, to determine the sufficiency of the data to support the claim of "inhibiting structural progression"; and thirdly, to determine the robustness of the data in supporting the claim of "improving physical function".

The efficacy of certolizumab was assessed by a number of means, which were appropriate, clinically meaningful, and relevant to the sponsor's application. The selected endpoints use well accepted, validated metrics that have served as the basis for previous published studies in RA management, and are consistent with the published guidelines recommended by regulatory authorities.

Pivotal efficacy study - STUDY CDP870-027 (RAPID 1)

The RAPID 1 Study was a prospective, multicentre, randomized, double-blind, active comparator-controlled, parallel-group, study of 52 weeks duration in subjects with active, adult-onset RA of at least 6 months (but less than 15 years) duration who have had an incomplete response to MTX. Subjects were randomized to one of three treatment groups in a 2:2:1 ratio: certolizumab 200 mg q2w (preceded by 3 loading doses of 400 mg q2w), certolizumab 400 mg q2w, or placebo injections with 0.9% preservative free saline solution. All patients received weekly background oral MTX at a dose of at least 10 mg/week (stable dose for at least 2 months prior to entry). All subjects continued their MTX treatment (with [69% of subjects] or without oral folic acid supplementation) throughout the trial at the same dose as at entry unless there was a need to reduce the MTX dose for suspected or actual toxicity reasons. As such, usual therapeutic doses of MTX were utilized (at least 10 mg/week, and up to 25mg/week).

The RAPID 1 Study was conducted in 147 study sites in 22 countries (mainly in the USA, Central and South America, and Eastern Europe) between 2005 and 2006. The main enrolment eligibility required that subjects be >18 years of age with a diagnosis of active, adult-onset RA as defined by the 1987-revised ACR criteria (>8 swollen joints out of 66 joints assessed, and >8 tender joints out of 68 joints assessed, and either erythrocyte sedimentation rate (ESR) 30 mm/hr or greater, or C-reactive protein (CRP) >15mg/L) with a disease duration of at least 6 months but less than 15 years.

Overall, the study population is externally valid but some limitations need to be considered. For example, patients with the following characteristics were excluded:- history of chronic infection or recent serious infection (including Herpes Zoster), positive serology for hepatitis B or C virus, history of non-cutaneous malignancy, or significant underlying cardiac, pulmonary, or renal conditions.

Objectives

The two primary efficacy endpoints in the RAPID 1 Study were to assess the efficacy of the 2 dose regimens of certolizumab in combination with MTX, versus MTX alone, for the following variables:

- Proportion of subjects who achieved an ACR 20 response at week 24 (a measure of treating the signs and symptoms of active RA); and
- Change from baseline in the modified Total Sharp Score (mTSS) at week 52 (a measure of inhibiting the progression of structural damage associated with RA).[2]

[2] Total Modified Sharp Score (TMSS) is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

Primary efficacy results

The analysis of both primary endpoints demonstrated that lyophilized certolizumab q2w (in either the 200 mg or 400 mg dose) with background MTX is statistically superior in a clinically meaningful level to treatment with MTX alone. In addition, the pair-wise statistical comparison of the efficacy data between the 2 certolizumab maintenance dose groups indicates that the 400 mg q2w dose does not confer a statistical advantage over the 200 mg q2w dose regimen.

A summary of the ACR response rates at week 24 is presented in Table 4.

Following 24 weeks of treatment, 58.8% (228/388) of subjects who received certolizumab 200 mg + MTX, and 60.8% (236/388) subjects who received certolizumab 400 mg + MTX achieved an ACR 20 response compared to 13.6% (27/198) of subjects who received MTX + placebo injections ($p<0.001$ for both certolizumab arms versus MTX alone). In comparison to placebo injections + MTX, the odds ratio for achieving an ACR 20 response at week 24 was significantly greater than 1.0 ($p<0.001$) for both certolizumab-treated groups (9.2 [97.5% CI of 5.5, 15.6] for certolizumab 200 mg and 10.1 [97.5% CI of 6.0, 17.0] for certolizumab 400 mg). Similar statistically significant ($p<0.001$) results favouring each certolizumab dose group over the control arm were demonstrated for ACR 50 responses (37.1% for certolizumab 200 mg and 39.9% for certolizumab 400 mg compared to 7.6% for MTX alone) and ACR70 responses (21.4% for certolizumab 200 mg and 20.6% for certolizumab 400 mg compared to 3.0% for MTX alone) at week 24. The statistical and clinical benefit of each certolizumab dose treatment in comparison to placebo injections + MTX was maintained up to week 52 for the ACR 20, ACR 50 and ACR 70 response rates. The small differences in the ACR response rates between the 2 doses of certolizumab was not statistically significant ($p<0.05$) nor clinically meaningful.

Table 4 ACR Response – Intent to Treat (ITT) Population

	Placebo + MTX (N = 199)	CZP 200 mg + MTX (N = 393)	CZP 400 mg + MTX (N = 390)
ACR-20			
Week 24			
n	198	388	388
Responder	27 (13.6%)	228 (58.8%)	236 (60.8%)
Odds Ratio vs. PBO+ MTX[(a)] [97.5% CI][(b)]		9.2 [5.5, 15.6]	10.1[6.0, 17.0]
P-value		<0.001	<0.001
Week 52			
n	198	392	388
Responder	26 (13.1%)	208 (53.1%)	213 (54.9%)
Odds Ratio vs. PBO+ MTX[(a)] [95%CI] [(b)]		7.7 [4.9, 12.2]	8.3 [5.2, 13.1]
P-value		<0.001	<0.001
ACR-50			
Week 24			
n	198	388	388
Responder	15 (7.6%)	144 (37.1%)	155 (39.9%)
Odds Ratio vs. PBO+ MTX[(a)] [95%CI] [(b)]		7.6 [4.3, 13.4]	8.5 [4.8, 15.1]
P-value		<0.001	<0.001
Week 52			
n	198	392	388
Responder	15 (7.6%)	149 (38.0%)	155 (39.9%)
Odds Ratio vs. PBO+ MTX[(a)] [95%CI] [(b)]		7.7 [4.3, 13.5]	8.3 [4.7, 14.6]
P-value		<0.001	<0.001
ACR-70			
Week 24			
n	198	388	388
Responder	6 (3.0%)	83 (21.4%)	80 (20.6%)
Odds Ratio vs. PBO+ MTX[(a)] [95%CI] [(b)]		9.2 [3.9, 21.7]	8.7 [3.7, 20.5]
P-value		<0.001	<0.001
Week 52			
n	198	392	388
Responder	7 (3.5%)	83 (21.2%)	90 (23.2%)
Odds Ratio vs. PBO+ MTX[(a)] [95%CI] [(b)]		7.6 [3.4, 16.8]	8.5 [3.8, 18.7]
P-value		<0.001	<0.001

[(a)] Odds ratio: CZP/placebo calculated using logistic regression with factors for treatment and region.
[(b)] Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
Note: Patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards.
Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo

A summary of the change from baseline in mTSS at week 52 is presented in Table 5.

Table 5: Changes in Baseline in mTSS at Weeks 24 and 52 – ITT Population

	Placebo + MTX (N = 199)	CZP 200 mg + MTX (N = 393)	CZP 400 mg + MTX (N = 390)
Baseline mTSS			
n	199	391	389
Mean (SD)	39.0 (44.5)	38.4 (49.4)	38.3 (47.1)
Median [Q1, Q3]	21.0 [7.5, 53.0]	20.0 [5.5, 49.0]	19.0 [6.5, 52.0]
Change from Baseline at Week 24			
n	180	353	355
Mean (SD)	1.3 (3.8)	0.2 (3.2)	0.2 (4.2)
Median (Q1/Q3)	0.0 (0.0, 2.0)	0.0 (-0.5, 0.5)	0.0 (-0.5, 0.5)
Difference[(a)] vs. PBO+ MTX[(b)]		-0.5	-0.5
95% CI for Difference, p-value[(c)]		[-0.8, 0.0], <0.001	[-0.7, 0.0], <0.001
% Inhibition vs. Placebo + MTX[(d)]		87%	83%
Change from Baseline at Week 52			
n	181	364	363
Mean (SD)	2.8 (7.8)	0.4 (5.7)	0.2 (4.8)
Median (Q1, Q3)	0.0 (0.0 - 4.4)	0.0 (-0.5, 0.5)	0.0 (-0.5, 0.5)
Difference[(a)] vs. PBO+ MTX[(b)]		-0.5	-0.6
97.5% CI for Difference, p value[(c)]		[-1.5, 0.0], <0.001	[-1.5, 0.0], <0.001
% Inhibition vs. Placebo + MTX[(d)]		85%	92%

[(a)] The differences presented are "CZP 200 mg/400 mg + MTX minus PBO + MTX."
[(b)] Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact).
[(c)] ANCOVA on the ranks with region and treatment as factors and rank Baseline as a covariate.
Abbreviations: SD=standard deviation; CI=confidence interval; MTX=methotrexate; PBO=placebo; Q1=lower quartile (25th percentile); Q3=upper quartile (75th percentile)
[(d)] % inhibition = (1 - (change from Baseline in mTSS in active treatment/change from Baseline in mTSS in control treatment))*100

An increase in the mTSS is indicative of disease progression and treatments that limit disease progression would show little change in the mTSS over time. Following 52 weeks of treatment, patients treated with certolizumab 200 mg + MTX (n=364) had a mean increase of 0.4 Sharp units (Standard Deviation [SD] 5.7; 97.5% CI -1.5, 0.0) and 0.2 Sharp units (SD 4.8; 97.5% CI -1.5, 0.0) in subjects treated with certolizumab 400 mg + MTX (n=363), compared to 2.8 Sharp units (SD 7.8; 97.5% CI not available) in subjects treated with placebo injections + MTX (n=181; p<0.001 for both certolizumab comparisons by rank analysis). The mean difference of at least 2.4 Sharp units over 52 weeks of therapy between the certolizumab treatment groups and MTX alone group is clinically meaningful. The small difference between the 2 doses of certolizumab was not statistically significant (p>0.05) at week 52.

Secondary efficacy results

The ACR 20, 50 and 70 response rates at week 24 and 52 provide a consistent pattern of greater improvements for both doses of the certolizumab + MTX compared to MTX alone.

A greater proportion of patients in both certolizumab dose groups achieved major clinical response than the placebo + MTX group.

Individual components of the ACR response criteria at weeks 24 and 52 showed a similar pattern of response to therapy as the overall composite response level with both doses of certolizumab being statistically superior to MTX alone (p<0.001 for all pair-wise criteria comparisons). There was no statistically significant difference between both treatment doses of certolizumab for any of the individual ACR criteria.

Mean change in DAS 28 from baseline and EULAR Response Criteria at week 52. Subjects who received certolizumab + MTX demonstrated a statistically greater reduction in the mean change from baseline in DAS 28 (-2.5 for certolizumab 200 mg + MTX, and -2.6 for certolizumab 400 mg + MTX) compared to subjects treated with MTX monotherapy (-0.7;

p<0.001 for both comparisons with certolizumab treatment). Subjects who received either dose of certolizumab + MTX displayed higher rates of EULAR response compared to subjects treated with MTX alone (p<0.001 for both pair-wise comparisons).[3] [4]

Change from baseline in the Erosion Score and Joint Space Narrowing Score at week 52.[2] A similar trend was observed in the individual components of the mTSS (that is erosion score [ES] and JSN score) as was seen for the primary radiological endpoint with certolizumab + MTX combination therapy in either dose regimen being statistically superior to MTX monotherapy. This pattern was seen at both 24 and 52 weeks of therapy). The same pattern was true for the JSN score at 52 weeks.

Proportion of subjects with no Radiographic Progression at week 52. 51.8% (103/199) of patients who received placebo injections had no radiographic progression (defined as mTSS score of <0.0) compared to 69.0% (271/393) and 72% (280/390) of subjects treated with certolizumab 200 mg and 400 mg, respectively.

Change in Physical Functioning. Subjects who received certolizumab + MTX combination therapy demonstrated a statistically greater improvement (that is decrease) in the HAQ-DI (-0.60 units for certolizumab 200 mg and -0.63 units for certolizumab 400 mg) compared to subjects who received MTX monotherapy (-0.18 units; p<0.001 for both comparisons). The difference of at least -0.42 is considered clinically meaningful.

Other measures:

- Change in Mental Component of SF-36.[5] Patients in the certolizumab 200 mg and certolizumab 400 mg groups recorded a statistically significant (p<0.001) mean change from baseline in the mental component of the SF-36 following 52 weeks of treatment.
- Change in Tiredness. Significantly greater reductions in tiredness were recorded in both certolizumab groups at all time points (from week 1 through to week 52) as measured by the FAS and SF-36 Vitality domain compared to MTX monotherapy (p<0.001).
- Change in Productivity. Productivity within and outside the home as assessed by the WPS was improved in both certolizumab treatment groups in comparison to MTX monotherapy as early as week 4 and this was maintained until 52 weeks of study treatment.

Efficacy conclusions

The efficacy data from this pivotal study (RAPID 1) indicates that certolizumab + MTX (in either the 200 mg q2w or 400 mg q2w dose regimen, using the lyophilized formulation) is statistically superior by a magnitude of clinical importance to MTX monotherapy for the treatment of the signs and symptoms of active RA, as well as the inhibition of structural progression. The efficacy outcomes between the 2 doses of certolizumab are comparable for clinical endpoints indicating no additional benefit from the higher maintenance dose regimen of 400 mg q2w.

[3] DAS = Disease activity score and DAS28 is a measure of the activity of rheumatoid arthritis. The DAS is based upon treatment decisions of rheumatologists in daily clinical practice.
[4] EULAR response criteria = The EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.
[5] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

Pivotal efficacy study - STUDY CDP870-050 (RAPID 2)

The RAPID 2 Study was a multicentre, randomized, double-blind, active comparator-controlled, parallel-group, study of 24 weeks duration in subjects with active, adult-onset RA of at least 6 months (but less than 15 years) duration who have had an incomplete response to MTX. Subjects were randomized to one of three treatment groups in a 2:2:1 ratio: certolizumab 200 mg q2w (preceded by 3 loading doses of 400 mg q2w), certolizumab 400 mg q2w, or placebo injections with 0.9% preservative free saline solution. All patients received weekly background oral MTX at a minimum dose of 10 mg/week (and up to 25mg/week), and in a stable dose for at least 2 months prior to entry. If oral folic acid supplementation was a prior treatment (63.2% [391/619] of subjects) then it was continued throughout the trial at the same dose.

The RAPID 2 Study was conducted in 76 study sites in 13 countries (mainly in Russia, Baltic States and Eastern Europe) between 2005 and 2006. The main enrolment eligibility required that subjects be >18 years of age with a diagnosis of active, adult-onset RA as defined by the 1987-revised ACR criteria. Patients were to have received prior treatment with MTX for at least 6 months prior to the baseline visit with a stable dose of at least 10 mg/week for the 2 months immediately prior to study entry. The other major eligibility requirements were identical to those of the RAPID 1 Study.

Objectives

The primary efficacy objective in the RAPID 2 Study was to assess the efficacy of the 2 dose regimens of certolizumab in combination with MTX, versus MTX alone, in the treatment of the signs and symptoms of RA. The primary criterion for this evaluation was the proportion of subjects between the 3 treatment groups who achieved an ACR 20 response at week 24.

Primary Efficacy Results

The primary efficacy endpoint of the ACR 20 response rate at week 24 was achieved. Specifically, 57.3% (141/246) of subjects who received certolizumab 200 mg + MTX, and 57.6% (141/245) subjects who received certolizumab 400 mg + MTX achieved an ACR 20 response compared to 8.7% (11/127) of subjects who received MTX + placebo injections ($p<0.001$ for both certolizumab arms versus MTX alone) (Table 6). In comparison to placebo injections + MTX, the odds ratio for achieving an ACR 20 response at week 24 was significantly greater than 1.0 ($p<0.001$) for both certolizumab treated groups (14.4 [97.5% CI of 6.7, 31.0] for certolizumab 200 mg and 14.3 [97.5% CI of 6.7, 30.8] for certolizumab 400 mg).

However, just like the RAPID 1 Study, the interpretation the above results requires the consideration of some caveats. Because of the study design in which non-responders at weeks 12 and 14 were withdrawn from the study at week 16 and designated “treatment failures” only 18.9% (24/127) subjects in the MTX monotherapy group had an opportunity to achieve ACR response at week 24.

This design also probably explains the very low rate of ACR 20 response in the placebo injection + MTX group compared to the similar treatment arm in other clinical trials of biologic agents for RA.

None of the treatment-by-subgroup interactions (at the 10% level) was found to be statistically significant in the subgroup analyses for the ACR 20 response at 24 weeks. The subgroups assessed included age at baseline (65 years or > 65 years), gender, race (Caucasian, non-Caucasian), weight quartiles, body mass index, duration of RA (<3 years or > 3 years), ESR and CRP at baseline, MTX dose at baseline (<10 mg/week or > 10 mg/week), previous anti-TNF use (yes or no), rheumatoid factor (RF) at baseline (positive or negative), and corticosteroid use at baseline.

Table 6: ACR Response at Week 24 – ITT Population

	Placebo + MTX (N = 127)	CZP 200 mg + MTX (N = 246)	CZP 400 mg + MTX (N = 246)
ACR-20			
Week 24			
n	127	246	245
Responder	11 (8.7%)	141 (57.3%)	141 (57.6%)
Odds Ratio vs PBO+MTX [a]		14.428	14.332
97.5% CI for Odds Ratio [b] [c]		[6.711, 31.020]	[6.669, 30.800]
p-value [b]		<0.001	<0.001
ACR-50			
Week 24			
n	127	246	245
Responder	4 (3.1%)	80 (32.5%)	81 (33.1%)
Odds Ratio vs PBO+MTX [a]		14.827	15.303
95% CI for Odds Ratio [b] [c]		[5.287, 41.581]	[5.457, 42.915]
p-value [b]		<0.001	<0.001
ACR-70			
Week 24			
n	127	246	245
Responder	1 (0.8%)	39 (15.9%)	26 (10.6%)
Odds Ratio vs PBO+MTX [a]		23.848	15.458
95% CI for Odds Ratio		[3.233, 175.896]	[2.070, 115.417]
p-value [b]		0.002	0.008

[a] Odds ratio: CZP/placebo calculated using logistic regression with factors for treatment and region.

[b] Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.

[c] p<0.001

Note: Patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards.

Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo

Secondary efficacy results

To support the claim of improving the signs and symptoms of RA the study also examined the ACR 50 and 70 response rates between the 3 treatment groups at week 24. Similar statistically significant (p<0.001) results favouring each certolizumab dose group over the control arm were demonstrated for ACR 50 responses (32.5% for certolizumab 200 mg and 33.1% for certolizumab 400 mg compared to 3.1% for MTX alone) and ACR 70 responses (15.9% for certolizumab 200 mg and 10.6% for certolizumab 400 mg compared to 0.8% for MTX alone) at week 24. The ACR 20, 50 and 70 response rates at week 24 provide a consistent pattern of greater improvements for both doses of the certolizumab + MTX compared to MTX alone.

At 24 weeks, the individual components comprising the ACR response showed a similar pattern of response to therapy as the overall composite response level with both doses of certolizumab being statistically superior to MTX alone (p<0.001 for all pair-wise criteria comparisons).

Efficacy conclusions

The efficacy data from this pivotal study (RAPID 2) indicates that certolizumab + MTX (in either the 200 mg q2w or 400 mg q2w dose regimen, using the optimized liquid formulation) is statistically superior in a clinically meaningful way to MTX monotherapy for the reduction of the signs and symptoms of active RA. However, the efficacy outcomes between the 2 doses of certolizumab are comparable for clinical endpoints.

Supporting efficacy study – STUDY CDP870-011 (FAST 4WARD)

The 24 week FAST 4WARD (eFficAcy and Safety of certolizumab– 4 Weekly dosAge in RheumatoiD arthritis) Study was designed to evaluate the efficacy of certolizumab 400 mg q4w as a monotherapy treatment. It was randomized, double-blind, placebo-controlled trial involving patients with active, adult-onset RA of at least 6 months duration who had previously failed (that is lack of efficacy) or were intolerant of at least 1 DMARD.

The FAST 4WARD Study was conducted in 36 study sites in 3 countries (USA, Czech Republic and Austria) between 2003 and 2004. Sites in the USA contributed 75% (165/220) of the total patients. Main eligibility requirements were subjects needed to be 18-75 years of age with a diagnosis of active, adult-onset RA as defined by the 1987 ACR criteria. Patients were to have received prior treatment with at least 1 DMARD and have a history of failure to adequately respond. All patients were to discontinue DMARDs at least 28 days prior to entry, or at least 5 half-lives (whichever was longer) in the case of leflunomide.

Objectives

The primary efficacy outcome in the FAST 4WARD Study was the proportion of subjects between the 2 treatment groups who achieved an ACR 20 response at week 24 (modified ITT population).

Primary efficacy results

The ACR 20 response rate at week 24 was 45.5% (50/111) for the treatment group which received certolizumab 400 mg compared to 9.3% (10/109) for subjects who received placebo injections ($p<0.001$).

Secondary efficacy results

At week 24, the ACR 50 and 70 Response rates for the 2 treatment groups showed a statistically significant ($p<0.001$) result favouring the certolizumab group over placebo. The percentage of patients achieving an ACR 50 response was 3.7% (4/109) for placebo and 22.7% (25/111) for certolizumab 400 mg. Only 6 patients reached an ACR 70 response and all of these subjects received treatment with certolizumab.

The individual components of the ACR response showed a similar pattern of benefit with certolizumab therapy compared to placebo.

Efficacy conclusions

The efficacy data from the FAST 4WARD study indicates that over 24 weeks of treatment, certolizumab (400 mg q4w dose regimen, using the lyophilized formulation) is statistically superior in a clinically meaningful way to placebo for the reduction of the signs and symptoms of active RA in patients who have previously failed to respond or are intolerant of DMARD therapy.

Supporting efficacy study – STUDY CDP870-014

This was a 24 week study designed to evaluate the comparative efficacy of certolizumab 400 mg q4w in combination with MTX 15-25mg/week (doses as low as 10 mg/week were permitted if reduced for toxicity reasons) versus MTX alone in patients with RA who were partial responders to MTX (stable dose for at least 8 weeks prior to the first dose of study medication). It was conducted as a randomized, double-blind trial involving patients with active, adult-onset RA (as per the definition in the pivotal studies) of at least 6 months duration.

The CDP870-014 Study was conducted in 43 study sites in 7 countries (Austria, Belgium, Czech Republic, Germany, Ireland, USA and Great Britain) between 2002 and 2004. Sites in Germany (39%, 96/247) and Great Britain (18.6%, 46/247) contributed the majority of

patients. Main eligibility requirements were subjects needed to be 18-75 years of age with a diagnosis of active, adult-onset RA as defined by the 1987 ACR criteria. Patients were to have received prior treatment with MTX for at least 6 months in total (stable dose of 15-25mg/week for at least 8 weeks prior to study entry) and have a history of insufficient response to that medication.

Objectives

The primary efficacy outcome in the CDP870-014 Study was the proportion of subjects (using the modified ITT population) who achieved an ACR 20 response at week 24.

Primary efficacy results

The ACR 20 response rate at week 24 was 45.9% (56/124) for the certolizumab + MTX group compared to 22.9% (27/119) for subjects who received placebo injections + MTX ($p<0.001$).

Secondary efficacy results

At week 24, the ACR 50 response rate for the 2 treatment groups showed a statistically significant ($p<0.001$) result favouring treatment with certolizumab + MTX compared with placebo injections + MTX.

The individual components of the ACR response showed a consistent pattern of benefit with certolizumab therapy compared to placebo injections. In further detail, the total swollen and tender joint counts showed that certolizumab was statistically superior to MTX alone at each measurement interval after week 4 during the study and continued to improve the longer patients participated in the study.

Efficacy conclusions

The efficacy data from the CDP870-014 study indicates that over 24 weeks of treatment, certolizumab (400 mg q4w dose regimen, using the lyophilized formulation) when added to background MTX treatment is statistically superior in a clinically meaningful way to continuing MTX alone for the reduction of the signs and symptoms of active RA in patients who have had an inadequate response to typical doses of prior MTX therapy (10-25mg/week).

Open-label extension study – STUDY CDP870-015

This is a multicentre (71 sites in 7 countries) open-label extension study in patients with RA dosing with subcutaneous certolizumab 400 mg q4w (with or without concurrent MTX 15-25mg/week depending on the pre-treatment of individuals in the feeder studies). Patients were eligible for participation in this study if they completed at least 12 weeks of blinded treatment in the precursor studies (CDP870-011 and -014) without being withdrawn for a possible drug-related adverse event or non-compliance.

A total of 402 patients entered the study and received at least 1 dose of certolizumab. Of these, 192 patients had previously received placebo injections (+/- MTX) in the precursor study, and 210 patients had previously received certolizumab injections.

Objectives

The primary efficacy outcome in the CDP870-015 Study is the proportion of subjects who achieve an ACR 20, 50 or 70 response at any particular chosen time point. The main secondary efficacy endpoints of this study included the change from baseline in the HAQ-DI, SF-36 domains (particularly, the PCS), changes in productivity as measured by the WPS, and the effect of anti-certolizumab antibodies on ACR response.

Efficacy results

Overall, ACR 20 responder rates showed an initial improvement with certolizumab treatment during the open-label extension period, and then a progressive decline over time.

In particular, the ACR 20 response rate for patients previously involved in Study CDP870-011 initially increased from 56.0% at week 1 (of the open-label period) to 65.2% at week 36, but thereafter gradually declined to 43.8% by week 112.

The ACR 20 response rate for patients previously involved in Study CDP870-014 initially increased from 51.0% at week 1 to 66.7% at week 36, but thereafter gradually declined to 48.8% by week 112.

Table 7: Summary of ACR 20 Response Rates – Comparison to Baseline (Patients from Feeder Study CDP870 -011)

	Placebo in CDP870-011		CZP 400 mg in CDP870-011		
	Withdrawers[b] (N=60)	Completers[c] (N=28)	Withdrawers[b] (N=23)	Completers[c] (N=75)	Total (N=186)
Week 1					
n	59	28	23	72	182
Responders	24 (40.7%)	17 (60.7%)	7 (30.4%)	54 (75.0%)	102 (56.0%)
Week 4					
n	60	28	21	73	182
Responders	29 (48.3%)	14 (50.0%)	5 (23.8%)	52 (71.2%)	100 (54.9%)
Week 8					
n	57	28	20	73	178
Responders	26 (45.6%)	14 (50.0%)	6 (30.0%)	52 (71.2%)	98 (55.1%)
Week 12					
n	56	27	19	73	175
Responders	29 (51.8%)	14 (51.9%)	9 (47.4%)	50 (68.5%)	102 (58.3%)
Week 36					
n	46	27	15	70	158
Responders	27 (58.7%)	17 (63.0%)	9 (60.0%)	50 (71.4%)	103 (65.2%)
Week 52					
n	56	27	20	71	174
Responders	26 (48.4%)	11 (40.7%)	10 (50.0%)	49 (69.0%)	96 (55.2%)
Week 112					
n	60	28	23	74	185
Responders	22 (36.7%)	9 (32.1%)	9 (39.1%)	41 (55.4%)	81 (43.8%)

Source: Supplementary Table 3

[a] Baseline is defined as Baseline from the feeder Study CDP870-011.

[b] Withdrawers were defined as patients who withdrew from the feeder study at Week 12 and before Week 24, and who did not withdraw for a possibly related AE or for noncompliance. Patients who received investigational product at Week 8 and had a Withdrawal visit ≤ 2 weeks before their scheduled Week 12 were eligible.

[c] Completers were defined as patients who completed through Week 24 of the feeder study.

The ACR 50 response rates showed a similar pattern to the ACR 20 response rates for all types of group analysis in that there appeared to be a slight initial benefit which consistently diminished after 36 weeks of open-label treatment to week 112. Patient numbers achieving an ACR 70 response was too small to allow any meaningful interpretation of the efficacy outcomes.

Patients treated with certolizumab or placebo injections in the precursor studies reported similar consistent improvements in physical function as assessed by a decrease in the mean HAQ-DI score and SF-36 PCS from week 1 of the open-label extension period through to week 112. Similarly, improvements in productivity (both outside and inside the house) were consistently maintained or stabilized over the 112 weeks of follow-up for both groups of pre-treatment.

The incidence of patients developing anti-certolizumab antibodies during Study CDP870-015 was 29.7% (55/186) in patients enrolled from Study CDP870-011 and 20.5% (44/216) for patients recruited from Study CDP870-014. This result is consistent with the

observed effect of MTX on reducing the incidence of anti-certolizumab antibody formation, which is a phenomenon seen with other anti-TNF drugs. The development of anti-certolizumab antibodies appeared to have a detrimental effect of achieving or maintaining a certain level of ACR response in Study CDP870-015.

Efficacy conclusions

The efficacy data from the open-label extension Study CDP870-015 indicates that over prolonged periods of treatment (up to 112 weeks of therapy), certolizumab 400 mg q4w is moderately efficacious in inducing a reduction in the signs and symptoms of active RA in patients who have previously received placebo injections (+/- background MTX) but the benefit may not be sustained. Similarly, patients previously treated with certolizumab who continue their therapy initially maintain this response but it may not be sustained over longer periods of follow-up. Furthermore, the development of anti-certolizumab antibodies appears to reduce the likelihood of achieving or maintaining a response to certolizumab treatment.

Safety

There were 6 placebo-controlled studies:

- 2 Pivotal Studies –CDP870-027 (RAPID 1) & CDP870-050 (RAPID 2)
- 2 Supporting Studies –CDP870-011 & CDP870-014
- 2 Phase II Studies – CDP870-002 & CDP870-004
- There were also Interim Safety Reports available for 3 Open-Label Extension Studies: CDP870-015, CDP870-028 & CDP870-051.

The analysis of safety was performed on the modified ITT population which included all patients who received at least 1 dose of investigational medication. Adverse events (AEs) were classified according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Incidence tables were used to summarize AEs. Descriptive statistics and/or shift tables were used to summarize findings and changes for both dichotomous and categorical variables. Treatment-Emergent Adverse Events (TEAEs) were not routinely summarized by number of cases per 100 patient years for each treatment group in the individual studies but rather for the pooled database of the 4 phase III studies.

Extent and duration of exposure

In the 6 placebo-controlled studies, a total of 1774 patients (n=640 for certolizumab 200 mg q2w + MTX; n=635 for certolizumab 400 mg q2w + MTX; n=278 for certolizumab 400 mg q4w; n=221 for other doses of certolizumab) received certolizumab and this comprises the main (or pivotal) safety analysis.

In the 4 phase III studies, a greater percentage of subjects in the pooled certolizumab dose group (5.0%) experienced AEs leading to withdrawal compared with the placebo group (2.5%).

Adverse events (AEs)

In the 4 phase III, placebo-controlled studies, the majority of AEs experienced by subjects in each of the treatment groups were of mild or moderate severity, and were considered as either unrelated or unlikely to be related to the study drug. Nonetheless, a greater percentage of subjects in the certolizumab treatment groups experienced AEs considered to be related to certolizumab compared with those patients who received placebo injections. There was no difference in the incidence of AEs between the 200 mg and 400

mg q2w dose regimens (67.8% and 67.1%, respectively), while subjects who received certolizumab 400 mg q4w had the highest incidence of AEs (77.7%). The q4w dose regimen of certolizumab was evaluated in Studies CDP870-011 and -014, which were primarily conducted at sites in North America and Western Europe. In contrast, the q2w dosing regimen studies of certolizumab (CDP870-027 and -050) were primarily conducted at sites in Eastern Europe. Cultural differences in reporting adverse effects may be one potential explanation for this observed difference rather than the dosing regimen.

Treatment-emergent adverse events (TEAEs)

Common TEAEs that occurred in a greater percentage of subjects who received certolizumab compared with the placebo injections (that is a difference of at least 2-fold) were upper respiratory tract infections (17.6% versus 9.4%), lower respiratory tract and lung infections (5.6% versus 3.4%), musculoskeletal and connective tissue disorders (6.7% versus 4.2%), herpes viral infections (3.6% versus 1.2%), rashes, eruptions and exanthems (4.0% versus 1.5%), and vascular hypertensive disorders (5.1% versus 1.2%) (Table 8).

The incidence of related TEAEs was also higher in the all certolizumab dose group compared with the placebo group in the categories of infections (15.5% versus 7.6% in the placebo group), respiratory disorders (3.0% versus 1.4% in the placebo group), skin and subcutaneous tissue disorders (7.6% versus 2.3% in the placebo group), and vascular disorders (2.1% versus 0.8%).

Table 8: Pooled Data for Phase III Studies. Summary of adverse events in All System Organ Classes, Including High Level Terms For Which Event Incidence was ≥ 3% in Any CZP Treatment Group or Greater than in the Placebo Group – Placebo – Controlled Data – Adult Rheumatoid Arthritis.

Primary System Organ Class High Level Term	PBO N=647		CZP 200 mg q2w[a] N=640		CZP 400 mg q2w N=635		CZP 400 mg q4w N=278		All CZP Doses N=1774	
	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]
Hepatobiliary disorders	7 (1.1%)	2.87 3.26	16 (2.5%)	3.96 5.35	11 (1.7%)	2.64 3.54	2 (0.7%)	1.75 1.74	30 (1.7%)	3.05 4.00
Immune system disorders	4 (0.6%)	1.64 1.63	5 (0.8%)	1.22 1.46	6 (0.9%)	1.42 1.65	5 (1.8%)	4.39 4.34	20 (1.1%)	2.01 2.40
Infections and infestations	148 (22.9%)	72.13 94.66	239 (37.3%)	79.88 107.76	239 (37.6%)	76.62 103.06	103 (37.1%)	117.79 122.49	667 (37.6%)	90.58 114.62
Upper respiratory tract infections	61 (9.4%)	26.49 30.19	107 (16.7%)	29.11 37.22	101 (15.9%)	26.71 33.49	55 (19.8%)	55.30 57.34	313 (17.6%)	35.24 41.91
Urinary tract infections	29 (4.5%)	12.28 15.91	40 (6.3%)	10.24 11.68	46 (7.2%)	11.49 14.86	6 (2.2%)	5.26 5.21	103 (5.8%)	10.80 13.20
Lower respiratory tract and lung infections	22 (3.4%)	9.14 10.20	37 (5.8%)	9.32 9.49	37 (5.8%)	8.95 9.20	14 (5.0%)	12.43 16.51	100 (5.6%)	10.30 11.20
Bacterial infections NEC	11 (1.7%)	4.53 5.30	26 (4.1%)	6.46 7.05	29 (4.6%)	7.08 8.73	1 (0.4%)	0.87 2.61	59 (3.3%)	6.04 7.30
Viral infections NEC	8 (1.2%)	3.31 4.08	25 (3.9%)	6.26 6.57	19 (3.0%)	4.55 4.95	2 (0.7%)	1.75 1.74	47 (2.6%)	4.79 5.10
Herpes viral infections	8 (1.2%)	3.29 3.67	20 (3.1%)	4.98 7.78	26 (4.1%)	6.32 8.25	10 (3.6%)	8.87 8.69	63 (3.6%)	6.46 8.40
Infections NEC	6 (0.9%)	2.46 3.67	19 (3.0%)	4.73 5.59	13 (2.0%)	3.10 3.54	3 (1.1%)	2.63 2.61	38 (2.1%)	3.86 4.40
Injury, poisoning and procedural complications	34 (5.3%)	14.46 19.59	53 (8.3%)	13.76 18.73	58 (9.1%)	14.49 20.05	19 (6.8%)	17.25 18.24	145 (8.2%)	15.37 19.90
Investigations	66 (10.2%)	28.80 49.37	97 (15.2%)	26.53 42.08	113 (17.8%)	30.13 46.93	34 (12.2%)	31.91 53.86	273 (15.4%)	30.55 48.01
Liver function analyses	31 (4.8%)	13.08 25.30	44 (6.9%)	11.32 17.76	54 (8.5%)	13.61 20.75	12 (4.3%)	10.76 19.11	119 (6.7%)	12.58 19.90
Metabolism and nutrition disorders	7 (1.1%)	2.87 2.86	14 (2.2%)	3.44 5.35	15 (2.4%)	3.57 4.72	6 (2.2%)	5.26 6.08	45 (2.5%)	4.55 5.90
Musculoskeletal and connective tissue disorders	122 (18.9%)	57.05 78.75	104 (16.3%)	28.39 46.46	98 (15.4%)	25.88 42.21	51 (18.3%)	48.73 72.10	327 (18.4%)	36.75 59.71
Musculoskeletal and connective tissue signs and symptoms NEC	27 (4.2%)	11.48 15.91	38 (5.9%)	9.65 13.38	41 (6.5%)	10.05 12.97	21 (7.6%)	18.90 21.72	119 (6.7%)	12.40 15.90

Primary System Organ Class High Level Term	PBO N=647		CZP 200 mg q2w[a] N=640		CZP 400 mg q2w N=635		CZP 400 mg q4w N=278		All CZP Doses N=1774	
	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]
Neoplasms benign, malignant and unspecified (excl cysts and polyps)	6 (0.9%)	2.46 3.26	12 (1.9%)	2.95 4.14	9 (1.4%)	2.14 2.83	2 (0.7%)	1.74 2.61	28 (1.6%)	2.82 3.70
Nervous system disorders	76 (11.7%)	34.08 45.29	57 (8.9%)	14.83 21.65	62 (9.8%)	15.92 22.17	61 (21.9%)	62.28 83.40	220 (12.4%)	24.06 34.30
Headaches NEC	40 (6.2%)	17.18 20.81	34 (5.3%)	8.59 11.43	26 (4.1%)	6.33 8.96	36 (12.9%)	34.35 38.22	124 (7.0%)	12.97 17.00
Paraesthesias and dysaesthesias	11 (1.7%)	4.53 5.71	10 (1.6%)	2.46 3.41	11 (1.7%)	2.63 2.83	14 (5.0%)	12.61 18.24	39 (2.2%)	3.96 5.50
Neurological signs and symptoms NEC	12 (1.9%)	4.97 6.53	5 (0.8%)	1.23 1.22	9 (1.4%)	2.15 2.36	10 (3.6%)	8.86 11.29	32 (1.8%)	3.24 3.60
Pregnancy, puerperium and perinatal conditions	0	0	0	0	1 (0.2%)	0.24 0.24	0	0	1 (0.1%)	0.10 0.10
Psychiatric disorders	27 (4.2%)	11.33 17.14	21 (3.3%)	5.25 6.32	18 (2.8%)	4.32 5.42	12 (4.3%)	10.79 11.29	64 (3.6%)	6.56 7.60
Renal and urinary disorders	16 (2.5%)	6.62 12.65	30 (4.7%)	7.53 9.97	29 (4.6%)	7.08 11.79	10 (3.6%)	8.83 13.90	82 (4.6%)	8.46 12.00
Reproductive system and breast disorders	10 (1.5%)	4.11 4.90	18 (2.8%)	4.46 5.59	19 (3.0%)	4.59 6.84	16 (5.8%)	14.31 20.85	58 (3.3%)	5.93 8.20
Respiratory, thoracic and mediastinal disorders	39 (6.0%)	16.51 23.67	43 (6.7%)	11.02 15.81	51 (8.0%)	12.73 16.74	31 (11.2%)	28.80 36.49	151 (8.5%)	15.99 22.10
Upper respiratory tract signs and symptoms	7 (1.1%)	2.87 2.86	13 (2.0%)	3.20 3.65	8 (1.3%)	1.90 2.36	9 (3.2%)	8.00 7.82	42 (2.4%)	4.26 5.10
Skin and subcutaneous tissue disorders	36 (5.6%)	15.28 20.81	68 (10.6%)	18.07 24.33	73 (11.5%)	19.01 25.00	48 (17.3%)	46.35 57.34	239 (13.5%)	26.34 34.60
Rashes, eruptions and exanthems NEC	10 (1.5%)	4.12 4.08	22 (3.4%)	5.50 6.32	28 (4.4%)	6.82 7.78	13 (4.7%)	11.63 13.90	71 (4.0%)	7.31 8.60
Alopecias	1 (0.2%)	0.41 0.41	0	0	6 (0.9%)	1.43 1.41	9 (3.2%)	8.00 9.56	17 (1.0%)	1.71 2.10
Social circumstances	0	0	1 (0.2%)	0.24 0.24	0	0	0	0	1 (0.1%)	0.10 0.10
Surgical and medical procedures	7 (1.1%)	2.88 2.86	7 (1.1%)	1.71 1.70	10 (1.6%)	2.39 2.36	6 (2.2%)	5.26 6.95	27 (1.5%)	2.73 3.00

Primary System Organ Class High Level Term	PBO N=647		CZP 200 mg q2w[a] N=640		CZP 400 mg q2w N=635		CZP 400 mg q4w N=278		All CZP Doses N=1774	
	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]	n (%)	IR/ ER[b]
Vascular disorders	20 (3.1%)	8.37 9.79	54 (8.4%)	14.06 17.76	71 (11.2%)	18.11 22.17	14 (5.0%)	12.55 13.90	157 (8.9%)	16.80 20.20
Vascular hypertensive disorders NEC	8 (1.2%)	3.29 3.26	33 (5.2%)	8.35 10.22	44 (6.9%)	10.81 12.03	6 (2.2%)	5.28 6.95	91 (5.1%)	9.44 11.00

Note: CZP = certolizumab pegol; ER=event rate per 100 patient-years; excl = excluding; incl = including; IR=incidence rate per 100 patient-years; mg = milligrams; NEC=not elsewhere classified; PBO = placebo; q2w = every 2 weeks; q4w = every 4 weeks.
A subject experiencing more than 1 AE in a category is counted only once in that category.
[a] Three loading doses of 400 mg each followed by 200 mg every 2 weeks.
[b] Incidence rate is presented as number of cases per 100 patient-years. Event rate was calculated as (total number of events/total exposure in years) X 100.

Deaths and other serious adverse events

In the 4 main placebo-controlled studies, 9 of 1774 subjects (0.51%) who received certolizumab at any dose, compared with 1 of 647 subjects (0.15%) who received placebo,

died. However, the total duration of exposure for subjects receiving certolizumab was 957.4 patient-years compared with 224.9 patient-years in the placebo group (that is a 4.3-fold difference in exposure) which may explain the difference in absolute numbers.

Clinical summary and conclusions

The principal efficacy results for certolizumab in adult patients with RA can be summarized as follows:

- certolizumab 200 and 400 mg q2w dosing regimens (with background MTX) have shown a statistically significant and clinically meaningful reduction in the signs and symptoms of active RA (as demonstrated by improvements in the ACR 20, ACR 50 and ACR 70 responder rates) compared to control (placebo injections + MTX) in 2 pivotal clinical studies,
- One pivotal study demonstrated that certolizumab 200 and 400 mg q2w (with background MTX) can result in a significant inhibition in the progression of RA related structural damage at 1 year compared to control treatment, and this result was supported by a further blinded phase III study over a period of 6 months,
- The same certolizumab treatment regimens have shown significant improvements in RA related pain, physical function, health related quality of life, productivity, and levels of tiredness (when pre-defined as secondary efficacy outcome measures),
- The use of an initial loading dose regimen of certolizumab (400 mg q2w for 3 doses) in 2 pivotal phase III studies demonstrates a quicker onset of effect but confers no additional benefit beyond 12 weeks of continued treatment when compared to a non-loading regimen of certolizumab 200 mg q2w,
- The optimized liquid (proposed commercial product) and the lyophilized formulation demonstrated similar clinical efficacy when indirectly compared in 2 well conducted phase III studies of like design (CDP870-027 and -050)
- The efficacy of certolizumab monotherapy was seen in a single q4w dosing strategy study that revealed significant reductions in the symptoms and signs of active RA,
- The formation of anti-certolizumab antibodies (overall incidence ~7%) is associated with reduced efficacy, and that subjects given concurrent MTX (as opposed to no MTX) had a lower incidence of developing such antibodies, and
- The limited efficacy data available at present from a single reported open-label extension study suggest that over prolonged periods of treatment (of up to 112 weeks), the benefit of certolizumab in reducing the signs and symptoms of active RA may not be sustained in a small but significant number of individuals.

In summary, the efficacy dataset supports the sponsor's proposed maintenance dosing regimen of 200 mg q2w. Although the maintenance 400 mg q2w dose demonstrates efficacy over control treatment, the concept that the lowest effective dose should be utilized needs to be applied. Alternatively, when an every 2 week dose schedule is not possible, a dose of 400 mg q4w has shown sufficient efficacy. It is also recommended that patients receive concurrent MTX when it is tolerated. However, certolizumab monotherapy can be recommended as an alternative in MTX intolerant individuals as it has demonstrated sufficient efficacy in reducing the signs and symptoms of active RA. The loading regimen of 400 mg q2w for 3 initial doses provides short-term benefit (up to 12 weeks) over a non-loading regimen but the clinical significance of this response is debatable in a condition such as RA which requires many years of treatment.

The safety of certolizumab for the proposed RA indication was assessed by reviewing the data collected from several sources including the controlled and open-label clinical

studies, as well as several safety analyses of particular topics. In total, the certolizumab database has a total exposure of approximately 4000 patient-years for patients with RA, and approximately 6400 patient-years for all indications (including Crohn's disease and psoriasis). In general, certolizumab was well tolerated when given predominately in combination with MTX. The majority of adverse events were of mild or moderate severity, often self-limiting, and did not necessitate permanent withdrawal from treatment. The safety profile of certolizumab can be summarized as follows:-

- The overall incidence and pattern of treatment emergent adverse events with certolizumab in the controlled studies was consistent with expectations for the treated population and type of therapy,
- In the placebo-controlled studies, there was an increased incidence of serious adverse events in the certolizumab treatment groups with no certolizumab dose effect observed,
- The most common serious adverse events were infections which may be expected for this class of drug and treatment population. However, the data indicates that certolizumab is associated with a significantly increased risk of opportunistic infections, particularly tuberculosis, which was commonly disseminated or extra-pulmonary in nature,
- Adverse events leading to withdrawal were as expected for this population and class of drug, and did not appear to increase with longer-term certolizumab treatment,
- The overall mortality rate in the certolizumab studies was at the lower limit of expectations,
- The incidence of malignancy was consistent with expectations in the study population,
- Other particular adverse events occurred at a low but expected frequency in patients who received certolizumab treatment including the development of autoantibodies, lupus-like illnesses, herpes viral infections, cytopenias and abnormal liver function tests, and
- The development of anti-certolizumab antibodies did not appear to consistently correlate with an increased of adverse events (overall and specific type).

The sponsor's proposed certolizumab product for marketing in Australia is the optimized liquid formulation presented in commercially prepared pre-filled syringes. A patient's ability to self-inject using this product has only been assessed in a sub-group of patients (n=91) in Study CDP870-051. Although the absolute numbers are small, the incidence and pattern of adverse events, as well as anti-certolizumab antibody formation, did not suggest any clinically significant differences compared to when the same formulation of certolizumab was administered by healthcare professionals. As such, the clinical evaluator would not recommend deferment of the sponsor's requested indication in patients with RA on the basis of this particular matter because the results obtained from the larger patient studies (particularly, Study CDP870-050, and to a lesser extent, Study CDP870-051) are likely to be extrapolated with confidence. Nonetheless, the sponsor should be asked to partake in a post-marketing program evaluating the tolerability and safety of self-administered certolizumab using the commercial preparation, with a plan to report the findings to the TGA at regular intervals, and within 12 months of initial registration.

V. Pharmacovigilance findings

The TGA Office of Product Review (OPR) granted a waiver from the requirement for a Risk Management Plan for this application.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality data package has been fully evaluated from the perspectives of biochemistry/quality, viral/prion safety, sterility, containers and closures and endotoxin safety.

The Delegate endorsed the recommendation of the quality evaluator that the batch release testing of the first five batches be made a specific condition of registration of this product and also endorsed the recommendations of the quality evaluator with regard to amendments of the PI and CMI.

All quality issues have now been satisfactorily resolved.

Nonclinical

Overall, the toxicology studies conducted with certolizumab did not reveal any safety issue of clinical concern. Therefore, there are no non-clinical objections to the registration of Cimzia for the proposed indication provided that the draft Product Information is amended as outlined by the non-clinical evaluator.

Clinical

The clinical evaluator has recommended approval of the application.

The Delegate was satisfied that there is sufficient evidence to support certolizumab as both monotherapy and in combination with MTX, provided there is sufficient clarification in the PI concerning the issues above, namely that there was no head-to-head comparison of the 200 mg q2w and the 400 mg q4w regimens and the numerically lower response rates on the latter.

There is insufficient data to support an indication of "inhibiting the rate of progression of joint damage". There is only data to 52 weeks. While not requiring data showing evidence of maintenance of radiological effect to 2 years with full randomization and treatment blinding – this would be excessively onerous and in certain instances unethical – the TGA does require some evidence of maintenance of radiological effect to 2 years. Usually this is provided in the second year from open-label extensions.

The inclusion of clinical endpoint claims such as those referring to physical function, although examined in the Phase III trials, are more appropriately placed in the Clinical Trials section rather than in the Indications.

Risk-benefit analysis

The data included in this submission indicates that certolizumab has a favourable benefit: risk analysis in reducing the signs and symptoms of active rheumatoid arthritis in adult patients who have failed to respond to, or are intolerant of, conventional DMARDs (particularly methotrexate). Therefore, the Delegate recommended acceptance of the sponsor's application to register certolizumab for the requested indication of reducing the signs and symptoms of RA. However, the Delegate did not recommend the acceptance of the other 2 treatment claims on the basis of the current submitted dataset. For the inhibition of structural progression claim, the current controlled dataset is of inadequate

duration to meet regulatory standards. In general, regulatory agencies (including the TGA) require 2 years of controlled data with appropriate endpoints for a sponsor to include of inhibition of structural progression. However, the currently available one year radiographic data for certolizumab may be included in the clinical data for the product information. For the claim of improving physical function, the main reason for non-acceptance of this indication is that the studies did not specify such measures as primary outcome measures.

In accepting the above indication, the Delegate recommended two conditions of registration. Firstly, that the sponsor should provide the full study reports of all on-going extension studies to the TGA as soon as they are completed. Amendments to the approved safety and efficacy data may be required in light of additional information, particularly in relation to opportunistic infection and durability of response.

Secondly, the wording of the proposed indication should be amended as the sponsor's proposed indication wording is long and unwieldy, lacks fluency in understanding the indication (for example, it doesn't specify rheumatoid arthritis in the first paragraph), and is poorly congruous with the wording used for other anti-TNF therapies approved for use in Australia. The following wording to the indication was suggested:

Cimzia is indicated for reducing the signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients where the response to previous non-biological DMARDs has been inadequate. Cimzia can be used in combination with methotrexate, or alone in those patients intolerant of previous DMARDs.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the application with the following wording:

Cimzia is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients:

- *combined with methotrexate in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs), or*
- *as monotherapy in case of a contraindication or intolerance to methotrexate (see Dosage and Administration).*

ADEC noted that the maintenance doses recommended for registration, when combined with methotrexate, are 200 mg subcutaneously every 2 weeks or 400 mg subcutaneously every four weeks. It also noted that there was insufficient clinical data to support a 2 weekly certolizumab monotherapy dose recommendation at this time. Thus the recommended monotherapy maintenance dose is 400 mg subcutaneously every 4 weeks. Certolizumab should be used in combination with methotrexate, except in cases where methotrexate is not tolerated.

The ADEC agreed with the Delegate that it is not appropriate to include references to inhibiting the rate of progression of joint damage or improvement of physical function in the indications for registration and noted that the sponsor has agreed to the removal of both these claims from the indications. With respect to the claim of inhibiting the rate of progression of joint damage, the ADEC further noted that the TGA routinely requires 2 year data to support such a claim, but that in this case only 1 year data has been evaluated by TGA to date (although 2 year data is included in the pre-ADEC response, this data has not been evaluated by TGA and thus no claim can be made in the Product Information with respect to this endpoint).

ADEC further recommended that the specific conditions of registration should include:

- That the sponsor provide to the TGA as a Category 1 application, as soon as they become available, the full study reports of all on-going clinical studies and the *in vitro* study prompted by the aPTT abnormalities detected in the study RAPID 2,
- That the sponsor agrees to implement a Risk Management Plan in Australia that is acceptable to the TGA. This plan must include monitoring for skin cancers and autoimmune disorders including systemic lupus erythematosus,
- That the first five batches of Cimzia imported into Australia are not released for sale until:
  - samples of each batch have been tested and endorsed by the TGA Office of Laboratories and Scientific Services (OLSS) and/or
  - the manufacturer's release data have been evaluated and endorsed by OLSS.
- These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency, and
- That evidence of satisfactory shipping conditions to Australia for every batch of Cimzia imported into Australia is provided to OLSS. This condition will remain in place until the sponsor is notified officially in writing of any change.

The Committee additionally noted the sponsor's commitment to updating the product information to include a statement on paediatric malignancies once negotiations with the US FDA on the wording of the statement are completed.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cimzia solution for injection pre-filled syringe containing certolizumab 200 mg/mL with the following indication:

Cimzia is indicated for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.

- *combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDS) or*
- *as monotherapy in case of a contraindication or intolerance to MTX (see Dosage and Administration).*

Specific conditions of registration for Cimzia were as follows:

- that the sponsor provides to the TGA as category 1 applications, as soon as they become available, the full study reports of all on-going clinical studies and the *in vitro* study prompted by the aPTT abnormalities detected in the study RAPID 2
- that the sponsor implements a Risk Management Plan in Australia which includes the specific monitoring of skin cancers and autoimmune disorders including systemic lupus erythematosus
- that the first five batches of Cimzia imported into Australia are not released for sale until:
  - samples of each batch have been tested and endorsed by the TGA Office of Laboratories and Scientific Services (OLSS) and/or
  - the manufacturer's release data have been evaluated and endorsed by the OLSS.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency, and

- that evidence of satisfactory shipping conditions to Australia for every batch of Cimzia imported into Australia is provided to OLSS. This condition will remain in place until the sponsor is notified officially in writing of any change.

Attachment 1. Product Information

The Product Information approved for main Cimzia at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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