European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/664021/2009

ASSESSMENT REPORT

FOR

Cimzia

International Nonproprietary Name: certolizumab pegol

Procedure No. EMEA/H/C/001037

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant UCB Pharma SA submitted on 6 June 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Cimzia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 January 2008.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication treatment of active rheumatoid arthritis.

Scientific Advice:
The applicant received Scientific Advice from the CHMP for certolizumab pegol on 14 December 2006.

Licensing status:
Cimzia has been given a Marketing Authorisation in U.S.A on 13 May 2009.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Tomas Salmonson   Co-Rapporteur: János Borvendég

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 6 June 2008.
- The procedure started on 25 June 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2008.
- During the meeting on 23 October 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 October 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 February 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 April 2009.
- During the CHMP meeting on 23 April 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the meeting on 22-25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cimzia on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2009.

2   SCIENTIFIC DISCUSSION

2.1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder of unknown etiology that occurs in approximately 1% of the population. RA is more prevalent among women than men and usually develops in the fourth or fifth decades of life. RA is manifested by accumulation and activation of several cell systems; T-cells with release of T-cell derived cytokines; B-cells with subsequent autoantibody responses, and macrophage- and fibroblast-like cells which produce large amounts of proinflammatory cytokines. The resulting synovial inflammation underlies the cardinal manifestations of this disease, which include pain, stiffness, swelling, and tenderness in the joints followed by cartilage destruction, bone erosion, and subsequent deformities, resulting in impaired physical function. There may also be associated morbidity from nonarticular manifestations of RA, including fever, malaise, and pulmonary, ocular, and hematologic effects. Patients with RA experience a shorter life expectancy than the general population, and the increased mortality rates in RA are associated with clinical disease activity. A large proportion of the excess mortality in persons with RA is related to cardiovascular disease.

Despite early disease-modifying antirheumatic drug (DMARD) and/or biological therapy, approximately 30-40% of patients with established RA fail to respond adequately either to non-biologic DMARDs and 50-60% of patients fail to achieve a major clinical ACR response or good EULAR response. Even among responders, the majority do not achieve remission. Therefore, there is a role for new biological therapies in the treatment of RA.

TNFα is a cytokine with multiple biologic actions, including protection against bacterial, fungal, parasitic, and viral infections, modulation of cell growth, mediation of inflammatory responses and interaction in a network with other lymphokines to modulate cells involved in immune response. TNFα has been implicated in autoimmune and inflammatory diseases, e.g. in the pathogenesis of rheumatoid arthritis where overproduction of TNFα causes synovial inflammation and proliferation in addition to degradation of articular cartilage and bone. Anti-TNF therapies are approved in the EU for the treatment of e.g. RA, Crohn's disease (CD), ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

Certolizumab pegol (CDP870, CZP), the drug substance of Cimzia, is a recombinant, humanized, antibody Fab' fragment with specificity for human TNFα. 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 to that of the whole antibody. Certolizumab pegol is an inhibitor of TNFα.

Cimzia is a clear to opalescent, colourless to yellow sterile solution for injection containing 200 mg certolizumab pegol in one ml. The product is supplied in single-use, prefilled syringes containing 1 ml, i.e. 200 mg certolizumab pegol. Excipients are sodium acetate, sodium chloride and water for injections; the pH of the solution is approximately 4.7.

The application for marketing authorization for Cimzia was a complete independent application for a new active substance and based on a full dossier. The assessment has taken into account the recommendations provided in the relevant CHMP guideline within this area (Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis; CPMP/EWP/556/95).

The indication initially claimed by the applicant and approved by the CHMP is:

> *"Cimzia, in combination with methotrexate, is indicated for:*
> - *the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs 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."

The recommended starting dose of Cimzia for adult patients with rheumatoid arthritis is 400 mg s.c. at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks.

2.2   Quality aspects

Introduction

Certolizumab pegol (CDP870), the drug substance of Cimzia is a recombinant, humanized Fab' antibody fragment (CDP870 Fab') covalently bound to a maleimido terminated bis-methoxypoly (ethylene glycol) modified lysine, PEG2MAL40K, through a thioether linkage. The linkage of the CDP870 Fab' to polyethylene glycol is introduced in order to extend its plasma half-life to that of the whole antibody. The CDP870 Fab' is directed against TNF (alpha) and neutralizes the biological activity of TNF α. The CDP870 Fab' is produced in *Escherichia coli*. Following purification by standard chromatographic methods, the CDP870 Fab' is conjugated to PEG2MAL40K. A single molecule of PEG2MAL40K is covalently bound to each Fab' molecule. The resulting CDP870 Fab'-PEG2MAL40K conjugate is further purified and formulated in acetate buffer at acidic pH to yield the Certolizumab pegol drug substance.

The development of CDP870 drug substance has encompassed various site, scale, and manufacturing process changes.

The drug product is presented as a liquid formulation containing 200 mg/ml in a prefilled syringe. Each prefilled syringe is intended for single use.

PEG2MAL40K – Pegylation moiety

The PEG2MAL40K is a polymeric substance with a distribution of different chain lengths. The PEG2MAL40K moiety comprises two 20 kDA PEG chains linked to a reactive maleimide group.

The manufacturing process has been adequately described and information on in-process controls is provided. The manufacturing process is considered sufficiently validated.

Control of materials used in manufacture has been adequately described and specifications for all starting materials, solvents etc. are provided.

The reference standard of PEG2MAL40K has been adequately characterised. Impurities are satisfactorily described with respect to the origin of the impurity, fate of the impurity and analytical control.

The specification requirements are considered adequate and the related methods are sufficiently described and validated.

The batch analysis data presented meet the specifications for PEG2MAL40K and are considered acceptable.

Sufficient stability data are submitted to justify the proposed shelf life. Stability studies are presented for the intermediate PEG2NHS40KP, which may be stored before further use in the manufacture of PEG2MAL40K. The proposed expiry date in the indicated package is considered acceptable.

The stability studies on PEG2MAL40K address three batches of each batch scale which have been stored under argon and air. The proposed re-test period in the indicated package is considered acceptable.

Active Substance

General information
The light chain of Certolizumab pegol is composed of 214 amino acid residues and the heavy chain is composed of 229 amino acid residues. The two chains are linked via a disulfide bond between the cysteine at position 214 on the light chain (the C-terminus) and the cysteine in position 221 on the heavy chain. The PEG2MAL40K moiety is a polydisperse mixture of an average molecular weight of 40,000 Da that is covalently bound to the CDP870 Fab' fragment through the C-terminus.

The experimentally determined molecular mass of CDP870 Fab' is approximately 47.8kDa. The experimentally determined molecular mass of Certolizumab pegol is approximately 90.8 kDa, which is consistent with the addition of a single molecule of PEG2MAL40K per molecule of CDP870 Fab'.

By virtue of its manufacture in *Escherichia coli*, CDP870 Fab' is not glycosylated. No N-terminal heterogeneity has been identified; neither heavy nor light chains appear to be blocked at the N-terminus. C-terminal heterogeneity of both the heavy and light chains of CDP870 Fab' is minimal due to the positioning of the cysteine residues required for interchain disulfide bond and for PEGylation.

- Manufacture

Manufacturer
CDP870 Drug Substance is manufactured by Sandoz GmbH in Kundl, Austria.

Genetic development
The generation and control of the expression plasmid is described in sufficient detail. CDP870 is a humanized Fab' version of the murine HTNF40 antibody, which binds to human TNF α and is a potent neutralizer of TNF activity. Detailed flow charts of the construction of the expression plasmid are provided. Expression is under control of the tac promoter.

Cell Banking
Cell banks of an *E.coli* strain were manufactured using media that are free from material of human and animal origin. The generation of the producer cell line, the master cell bank (MCB) and the master working cell banks (MWCB) is adequately described. In addition, data on the characterisation of the producer cell line and the cell banks used in production are considered satisfactory in general. Acceptable protocols for the preparation and control of new MWCBs are included in the dossier.

Genetic stability
Testing of end-of-production cells (EOP)–and post-production cell bank (PPCB)–was performed to establish the genetic stability and robustness of the fermentation process. Analysis of copy numbers (copies/cell) from sub-cultured cells or directly from vials, plasmid retention, retention of expression construct, restriction digest and DNA sequence (post production cell bank) are sufficiently described.

Overall, acceptable information has been provided on genetics development, genetic stability and cell bank stability.

Cell culture and purification
The cell culture and purification process are documented in detail and a flow chart has been submitted.

Briefly, the CDP870 Drug Substance is produced during specific manufacturing campaigns, in which the Fab' is extracted, purified, and PEGylated. Manufacture is divided into steps grouped into three main areas which reflect the major activities: fermentation, primary isolation, and purification/PEGylation.

In conclusion, the drug substance manufacturing process is described in great detail, including information on the control of temperature, the acceptable range for operational controls, the compositions of buffers and media used, as well as the identification of in-process control tests and the specification/action limits by which they are controlled. Acceptable in-process controls are in place throughout the CDP870 drug substance manufacturing process.

Conditions for storage of process intermediates have been defined and the maximum time of storage has been specified.

Validation

The drug substance manufacturing process has been adequately validated demonstrating that the purification process consistently produces drug substance of reproducible quality that complies with the predetermined specification and in-process tests.

The studies conducted for validation of the production process are in most respects both well designed and reported. For those parts that refer to the identification and control of critical steps supplementary validation reports have been provided, giving satisfactory support to both, the in-process control system applied and the proposed operation ranges.

Manufacturing process development

The development of CDP870 Drug Substance has encompassed various site, scale, and manufacturing process changes. The majority of the process changes have 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 CDP870 Drug Substance, and to accommodate differences in various Drug Product formulations (e.g., protein concentration, final formulation buffer, pH).

There are in total nine CDP870 Drug Substance manufacturing processes which are considered comparable with regard to consistency of manufacture and with regard to the quality and stability of CDP870 Drug Substance produced.

Detailed information on each of the nine processes in way of manufacturing process description including information on animal-derived raw materials; analytical methods and specifications; summary of process batches; stability data and comparability in way of comparison of stability profiles, release testing and additional analytical characterisation of the process vs. the previous process is provided.

Process 9 was used for the production of CDP870 Drug Substance, 200 mg/mL (acetate buffer, pH 4.7) for Phase III clinical studies, ICH stability studies, and has been subject of the process validation data.

Characterisation

An exhaustive characterisation of CDP870 Fab' and CDP870 drug substance has been conducted on material representative of the commercial process (Process 9; acetate buffer, pH 4.7), revealing the structure of CDP870 Fab' and drug substance as well as product-related substances, product- and process-related impurities. Supporting characterisation data from Process 8 (lactate buffer, pH 5.0) and from the characterization of reference standards were provided. The methods used are considered as state of the art.

The structural and functional characteristics of CDP870 drug substance have been investigated using a wide variety of analytical tools including amino acid analysis, N-terminal sequencing, MALDI-TOF mass spectrometry, enzymatic and chromatographic methods, physical analyses, and binding and neutralization assays. In addition, forced degradation studies have been performed on CDP870 Drug Substance. Product related impurities have been studied by a range of methods including RP-HPLC/Isoquant-reaction, Peptide Mapping, RP-HPLC, CX-HPLC, and SE-HPLC.

Comparability studies have been performed between materials for product in the lyophilized and liquid formulation. The comparability studies included both drug substance and drug product, and consisted of side-by-side comparison of release data, results from the extended characterisation and stability data. In these studies, no significant difference was detected between drug substance in the lactate and the acetate formulation. However, as could be expected from the change in formulation, the

amounts of acidic and basic species are increased in the liquid formulation. These were classified by the applicant as product-related substances.

- Specification

Specifications
The specifications are adequately set and justified based on 3 standard deviations around the mean of release data of all batches used in the phase III clinical trials. The stability data indicates that there is no change on long term storage for CDP870 Drug Substance and hence a separate end of shelf- life specification has not been applied. The proposed release specifications have either been tightened or are the same as those applied to the phase III clinical trial material. The release specifications are considered acceptable. Product-related substances and impurities as well as process-related impurities are adequately controlled.

Analytical methods
All analytical methods for release testing of drug substance are adequately described. The use of the analytical methods in analyses of drug substance in the acetate formulation is generally satisfactorily validated. Concerns that were raised on the control in performance of the potency assay, and the sensitivity of the CEX-HPLC analyses have been satisfactorily addressed.

Reference standard
The reference material is adequately characterised. However, the current standard was derived from the previous process (lactate-formulation) and a new Primary Reference, sourced from a commercially released lot of CDP870 Drug Substance (acetate), will be created and qualified in accordance with the procedure presented in the dossier (see section 2.7).

Batch data
Extensive batch analysis data from more than 30 batches produced in process 8 and 9 have been provided. The data show that the proposed manufacturing process is capable of consistently producing drug substance.

Container closure system
The container closure system for CDP870 drug substance is sufficiently described.

- Stability

Adequate stability data were submitted to justify the proposed shelf life of the drug substance when stored at -70°C ±10°C. The stability of the drug substance has been extensively investigated on supportive and pivotal long-term stability batches. In general, results at all time points tested conform to the shelf-life specification and the data presented do not show a trend in degradation of the drug substance. The post approval stability protocol is acceptable.

Medicinal Product

Composition and container closure system
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/ml drug substance.

The excipients used in the formulation of the drug product are of pharmacopoeial quality. There are no excipients of human/animal origin in the drug product.

- Pharmaceutical Development

The liquid formulation development has been thoroughly described and the rationale for the selection of the formulation and container configuration has been adequately addressed and justified. During the pre-clinical and clinical studies several changes in manufacturing site and batch size have been

introduced. Besides the use of different drug substance concentrations and fill volumes, the major changes in development refer to the alternative use of a liquid and a lyophilised formulation. The commercial process for production of the liquid formulation in pre-filled syringes was developed in 2007. These changes are considered well described and adequate comparability studies have been performed.

- Manufacture of the Product

Manufacturer
The drug product is manufactured by Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany.

Manufacturing process
The drug product manufacturing process is described in sufficient detail including information on the control in operation, the compounding, filling and lyophilisation steps. Manufacture of drug product employs a straightforward process including conventional steps for compounding, sterile filtration, aseptic filling and stoppering. The critical steps are defined and controlled.

Process validation
Process Validation consisted of three consecutive batches covering the approximate minimum and maximum batch size. The validation of the entire process was achieved through the consecutive execution of three batches according to the established master batch record and ancillary process validation studies including: manufacturing support validation, equipment validation and cleaning validation.

- Product Specification

Product Specification
The selected parameters to control the drug product have been adequately justified and the release specifications are set reasonably tight.

Analytical methods
All methods for release testing of the drug product have been adequately described and are validated. The proposed limits are considered acceptable.

Batch data
Batch analysis data from eight batches of Cimzia in pre-filled syringes produced at the commercial manufacturing site confirm the consistency of the drug product manufacture.

- Stability of the Product

The stability data submitted sufficiently justify the shelf life declared in the product information. The stability of the drug product has been extensively investigated on supportive and commercial batches and based on the available data the Company originally claimed a shelf life of 24 months for drug product stored at $+5 \pm 3°C$. In response to the concerns raised on whether all future batches will remain within the approved specifications over the entire product lifetime, the applicant has reviewed the stability data and proposes a revised shelf life of 18 months which is considered acceptable.

The post approval stability protocol is acceptable. The applicant commits to place at least one batch of the drug product in long term stability study per year.

- Adventitious Agents

The non-viral safety of Cimzia is considered to be assured based on the precautions taken under manufacturing, the testing of raw materials and process steps.

The drug substance production substrate is bacterial in origin and is considered unlikely to be capable of supporting the propagation of adventitious viral contaminants.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The documentation provided with the application demonstrates consistent batch-to-batch production of Cimzia achieving a consistent quality for the drug substance and the drug product. The fermentation, purification and pegylation of the drug substance, Certolizumab pegol (CDP870), are adequately controlled and validated. The drug substance has been extensively characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. In addition, the viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. In general, appropriate drug substance and drug product specifications have been set.

2.3   Non-clinical aspects

Introduction

The non-clinical development strategy for certolizumab pegol was based on the pharmacological activity/selectivity of the molecule and the intended (s.c.) clinical route of administration. Based on the species specificity of target binding, the cynomolgus monkey has been selected as the main species for toxicity testing. The non-clinical programme meets the requirements of relevant with EU/ICH guidelines.

In non-clinical studies material derived from different manufacturing processes and different formulations (initial liquid formulation, lyophilised formulation) have been used; none of the non-clinical studiesy wereas performed with a batch from the process intended for marketing (new liquid formulation). In a new comparability studies submitted for the RA indication, no difference was seen between the first and second generation (new clinical liquid formulation) manufacturing processes of certolizumab pegol when binding to TNFα and competitive binding with human TNF receptor 1 to TNFα was evaluated. Also, *in vivo* (mouse model), no difference in neutralisation potency was seen between these materials.

The toxicology program included studies of single and repeat-dose toxicity, genotoxicity, developmental toxicity, and local tolerance. Within each area, main studies were done in compliance with GLP, including toxicokinetic data.

Pharmacology

- Primary pharmacodynamics

Certolizumab pegol binds soluble human TNFα (hTNFα) with high affinity (KD ~90 pM). Binding to transmembrane hTNFα was also shown. Certolizumab pegol neutralised hTNFα in the L929 cell assay (IC_{90} 4 ng/ml). It also inhibited lipopolysaccaride (LPS)-induced release of cytokines *in vitro* (IC_{50} 0.1-0.2 ng/ml). Certolizumab pegol did not bind TNFα from rodents, rabbit, guinea pigs and dog, but it inhibited TNFα from non-human primates, with at least a 1000-fold lower activity than against hTNFα. The cynomolgus monkey was selected for toxicity testing and the IC_{90} (L929 cell assay or a monkey fibroblast assay) for TNFα in this species was $100 - 362$ μg/ml. Data on interactions with the TNFα receptors (p55 and p75) are sparse, and preclude an estimation of actual potency.

The pharmacology of certolizumab pegol has been compared to other licensed anti-TNFα reagents, namely the whole immunoglobulins infliximab and adalimumab as well as the Fc-fused soluble receptor etanercept. BIAcore determined rank order of binding affinities for soluble recombinant human TNFα (rhuTNFα) was: etanercept (33.2 pM), certolizumab pegol (86.4 - 91.5 pM), adalimumab (158.3 pM) and infliximab (228.7 pM). All anti-TNFα reagents were potent neutralizers

of soluble and membrane rhuTNFα. Certolizumab pegol, infliximab and adalimumab completely inhibited the LPS-driven production of TNFα and IL-1β by the human monocytic cell line MM6 and primary monocytes in the *in vitro* system used, whereas etanercept only partially inhibited this effect.

Certolizumab pegol was studied in two *in vivo* models where normal mice or rabbits were challenged with hTNFα. In these models, certolizumab pegol inhibited hTNFα induced effects. Effective doses ranged from 3-3000 µg/kg. certolizumab pegol also protected against development of arthritis in one transgenic mouse, serving as a disease model for polyarthritis, at 10 and 30 mg/kg

- Secondary pharmacodynamics

CDC and ADCC measurements
In contrast to other anti-TNF agents, certolizumab pegol lacks an Fc fragment and is therefore expected to also lack effector functions. TNF6.5 cells were used as the target cells and rabbit serum was used as the source of complement for the assessment of complement dependent cytotoxicity (CDC). Cytotoxicity was assessed by uptake of the vital stain, PI and by the release of LDH. Antibody-dependent cell-mediated cytotoxicity (ADCC) induced by the anti-TNFα reagents was determined by incubating target TNF6.5 cells and PBMC-derived effector cells in RPMI 1640 on plates with various concentrations of the anti-TNFα reagents. As expected, certolizumab pegol did not induce either complement or cell-mediated lysis of target cells bearing TNFα.

Apoptosis induction
In a comparative *in vitro* studies performed by the applicant, certolizumab pegol did not cause any increase in cells exhibiting an apoptotic phenotype while for other anti-TNF agents a concentration-dependent increase was observed. Similar observations were made in neutrophil survival and degranulation tests.

- Safety pharmacology programme

Two *in vitro* GLP safety pharmacology studies have been conducted:

In a standard *in vitro* human tissue cross reactivity study, 3 and 10 µg/ml of certolizumab pegol did not result in any unexpected binding. A cynomolgus monkey cross reactivity study was not performed.

A blood compatibility study evaluated the compatibility of certolizumab pegol with human whole blood, plasma and serum. *In vitro*, certolizumab pegol did not cause haemolysis of whole blood from healthy donors, but dose-related erythrocyte clumping (from 0.33 mg/ml) and opalescence of plasma and serum (at 33 mg/ml). The NOEL for erythrocyte clumping (0.033 mg/ml) is below clinical plasma levels.

No *in vivo* safety pharmacology studies have been conducted with certolizumab pegol, however monitoring of potential undesirable pharmacological activity was incorporated in both the repeat dose toxicity studies and single dose Phase 1 clinical studies. The lack of formal non-clinical safety pharmacology studies are justified by the absence of any cross-reactivity of certolizumab pegol with human tissues and the lack of effect of certolizumab pegol on the safety pharmacology parameters assessed in repeat dose toxicity studies in cynomolgus monkeys and in the Phase 1 clinical studies.

- Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with certolizumab pegol. The applicant justified the lack of data by arguing that no potential pharmacodynamic drug interactions at the p55 and p75 TNF receptor level are considered likely, as certolizumab pegol should not be used with other anti-TNFα agents.

Pharmacokinetics

Certolizumab pegol is pharmacologically active in cynomolgus monkeys. Therefore, pivotal pharmacokinetic studies were conducted in this species. Additional data were generated early in development in the rat, a species in which certolizumab pegol is not pharmacologically active

Analyses of certolizumab pegol and anti-certolizumab pegol antibodies were made by ELISAs. The presence of certolizumab pegol in plasma interferes with the antibody analyses, and vice versa, which reduces the reliability of the pharmacokinetic data and the possibility to detect antibodies against certolizumab pegol. Analysis of the PEG moiety was performed in blood and urine using a NMR assay. The method identified PEG covalently bound to the Fab' fragment as well as 40 kDa PEG (i.e. the isolated PEG component).

In cynomolgus monkeys, certolizumab pegol appeared to have roughly linear pharmacokinetics. Although not formally studied, bioavailability after s.c. administration was estimated to be nearly complete. Addition of 40 kDa PEG to the Fab' fragment increases the elimination half-life and AUC when compared to the Fab' fragment alone or the Fab' added a 25 kDa PEG chain. The $T_{1/2}$ was 8.5-10.5 days after repeated dosing. The presence of anti-CDP870 antibodies appeared to result in shortened $T_{1/2}$ values. If antibodies were neutralising is unknown.

In a distribution study, presence of the PEG component was shown in all analysed tissues (liver, spleen, kidneys, heart, lungs, brain and mesenteric lymph nodes) following administration of certolizumab pegol and the rat equivalent cTNF3 PF to rats. The highest level of PEG was detected in the liver (7% of the dose administered). There was no indication of tissue uptake of PEG, associated with binding to membrane bound TNF alpha.

Due to the protein nature of the Fab' fragment, it is expected to undergo proteolysis and excretion via the urine. Limited data from SDS-PAGE analyses indicate that only 40 kDa material can be identified in the urine of rats. Thus, it appears that the Fab' is catabolised prior to excretion of the 2 x 20 kDa PEG chains linked via a lysine residue. The metabolic fate of the maleimide linker is less clear. Following administration of 400 mg/kg/week certolizumab pegol sc to rats for 12 weeks, the terminal $T_{1/2}$ for PEG was 24 days. The cumulative excretion was 65% in urine, and the total recovery (urine + feces) was 83%. Analyses of tissues from rats given a single 100 mg/kg dose showed similar clearance from tissues and urine.

cTN3 PF, a chimeric mouse/hamster PEGylated Fab' fragment that binds rat TNFα which was used for testing of reproductive toxicity, showed negligible placental transfer and milk excretion in rats. It was not detected in plasma of nursing pups. cTN3γ1, the parental complete antibody binding rat TNFα, passed the placenta to some extent (15%), and was excreted in milk (24%).

Toxicology

Species specificity
The cynomolgus monkey was selected as the main species for toxicity testing. *In vitro*, certolizumab pegol was at least 3,500 to 33,000 times less potent against TNFα from cynomolgus than human (IC_{90} of 362 and 0.1 µg/ml in the monkey fibroblast assay or IC_{90} 100,000 and 3 ng/ml in the murine fibroblast assay, respectively). Furthermore, distribution / tissue cross reactivity data for certolizumab pegol in the cynomolgus are lacking. Thus, certolizumab pegol was considerably less potent in binding monkey TNFα than human, and the excess of the plasma levels above IC_{90} for TNFα is 10,000-fold higher in patients than in the monkey studies. These facts may question the relevance of this model to fully identify effects related to inhibition of TNFα. Nevertheless, it is acknowledged that plasma levels in monkeys were above the IC_{90} for monkey TNFα and the plasma concentrations obtained resulted in saturation of membrane TNFα binding as well as binding of soluble TNFα. Furthermore, the clinical safety profile is considered adequately well established from experience with other anti-TNFα agents, and therefore these limitations are accepted.

In terms of the PEG-component, data in both the rat and monkey are of value. One concern of the CHMP related to the certolizumab pegol construct and the question whether binding to membrane bound TNFα may lead to targeted exposure of certain cells to the PEG component and whether such

potential effects would have been adequately covered by the available non-clinical data. The Applicant provided data supporting that the majority of cell uptake is not antigen dependent and that certolizumab pegol saturated membrane-bound TNFα on different cell types from human and cynomolgus monkey in a similar manner and at concentrations below those achieved in the toxicity studies.

A list of pivotal toxicology studies conducted with certolizumab pegol or its analogue, cTN3 PF, is presented in Table 1.

Table 1   Pivotal toxicology studies conducted for certolizumab pegol.

Study Type	Study Duration and Route of Administration	Species/Test species	Dose (mg/kg)
Repeat-dose toxicity	Once weekly iv infusion for 4 weeks (dosing on Days 1, 8, 15 and 22; necropsy Days 29 or 57)	Cynomolgus monkey	0, 50, 100 and 400
Repeat-dose toxicity	Once weekly sc dosing for 13 or 26 followed by 13 week treatment-free (necropsy at Weeks 13 or 26 at the end of treatment or in Weeks 26 and 39 treatment free periods)	Cynomolgus monkey	0, 10 and 100
Genotoxicity (bacterial mutation	-	*Salmonella typhimurium Escherichia coli*	*In vitro* Up to 4997 µg per plate
Genotoxicity (chromosome assay)	-	Human lymphocytes	*In vitro* Up to 5001 µg/mL
Genotoxicity (micronucleus assay)	Once daily iv bolus for 2 consecutive (24 hour harvest)	CD-1 mouse	*In vivo* 0, 104.1, 208.2 and 416.4
Reproduction and development (Fertility and early embryonic development)	Iv infusion: females dosed twice weekly weeks prior to pairing (with untreated during cohabitation and on G1[b] & G4 iv infusion: males dosed twice weekly during cohabitation (with untreated to necropsy at Week 10	Sprague Dawley rat	0, 20 and 100 mg/kg cTN3 PF[a]
Reproduction and development (Embryofetal development)	Iv infusion: females administered two or on G1 & G4; or G6, G9, G13 & G16	Sprague Dawley rat	0, 20 and 100 mg/kg cTN3 PF[a]
Reproduction and development (Prenatal and postnatal development)	iv infusion: females dosed on G6, G9, And G20 and on L2[c], L6, L9, L13, L16	Sprague Dawley rat	0, 30 and 100 mg/kg cTN3 PF[a]
Local tolerance	Single sc dose	Rat	0, 160 and 800
Local tolerance	Single sc dose	Rat	0 and 200 mg/dose
Local tolerance	Single sc dose	Rat	0 and 100 mg/dose
Other toxicity (Immunotoxicity)	Once weekly sc dosing for 52 weeks during Week 52 or 78)	Cynomolgus monkey	0, 50 and 100
Other toxicity	Single iv infusion (necropsy on Day 8)	Han Wistar rat	0, 100, 200, 400 and 1000
Other toxicity	Once daily iv infusion for 5 days (necropsy on Day 6)	Han Wistar rat	0, 50, 100 and 400
Other toxicity	Once daily iv infusion for 5 days (necropsy on Day 6)	Han Wistar rat	0, 44, 88 and 352

(a) CDP870 does not recognize murine or rat TNF , hence an analogous Fab' fragment to murine TNF , cTN3 PF, was used in reproduction and development studies
(b) Gestation Day
(c) Lactation Day

- Single dose toxicity

Cynomolgus monkeys were given a single i.v. infusion of 50, 100 or 400 mg certolizumab pegol/kg, and were observed for 28 days. There were no signs of overt toxicity or effects on general health of the animals. The no observed adverse effect level (NOAEL) was 400 mg/kg..

The maximal exposure attained was approximately 200-fold higher than that observed at the maximal recommended human dose (approximately 50 µg/ml) and is also well above the concentration (10 µg/ml) needed to neutralize the activity of cynomolgus monkey TNFα *in vitro*.

- Repeat dose toxicity (with toxicokinetics)

The pivotal repeat dose toxicity studies consisted of a 26-week repeat-dose toxicity study and a 52-week immunotoxicity study, both performed in cynomolgus monkeys. The animals were administered 10 and 100 mg/kg/week s.c. certolizumab pegol and 50 and 100 mg/kg/week s.c. in the 26- and 52-week study, respectively.

Decreases in platelets, white and red blood cells were found in the 52-week study. Increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) were observed in repeat i.v. dose studies conducted in monkeys and rats. APTT was also increased (30%) at both doses in the 52-week monkey study. The Applicant suggests that it may be related to the PEG moiety, based on published data. In an *in vitro* study, certolizumab pegol increased APTT in monkey plasma. The lowest concentration tested (200 µg/ml) prolonged APTT and is 4-fold above the estimated clinical exposure.

In rats and monkeys histopathology revealed cellular vacuolation, present mainly in macrophages, in a number of organs (lymph nodes; injection sites, spleen; adrenal; uterine, cervix; choroid plexus of the brain, and in the epithelial cells of the choroid plexus). These effects were partly reversible after 13 or 26 weeks without treatment. There were no other morphological changes or adverse findings associated with the cell vacuolation in the tissues.

The presence of foamy macrophages in various organs is likely related to the PEG-component. In a set of *in vitro* tests with this PEG, mouse and human macrophage viability, and some other *in vitro* parameters were generally not affected, but phagocytic ability was reduced for uptake of bacteria and fungi. The NOEL was 0.1 (Fab'PEG) and 1 mg/ml (PEG). Some inhibition of T-cell proliferation to toxoid challenge in a human cell system was seen (NOEL 1 mg/ml).

No effects on immune function were observed in the 52 weeks study. The reason why effects on the immune system similar to other anti-TNF agents were not seen with certolizumab pegol is unknown, but it may be suspected that there is a relation to the lower potency of certolizumab pegol for monkey than human TNFα.

Two low dose animals in the 52 weeks study had detectable antibodies, but the number of positive samples may be underestimated since the presence of certolizumab pegol in plasma interferes with antibody analyses.

- Genotoxicity

Certolizumab pegol displayed no genotoxic potential in a standard test battery. The PEG construct is not considered to pose genotoxic concern, and thus the data provided were considered sufficient.

- Carcinogenicity

No conventional carcinogenicity testing was performed with certolizumab pegol, which was acceptable considering the nature of the compound and the lack of pharmacological activity and immunogenicity of certolizumab pegol in species normally used for such testing.

However, based on the current knowledge about TNFα in the context of malignancies/lymphoma, the concern related to long-term suppression of the immune function due to TNFα inhibition as well as

signals from clinical experience with the other anti-TNFα agents, the possible risk for the development of lymphomas or other malignancies in patients treated with TNF antagonists is reflected in the SPC and PL, and warrants post marketing surveillance.

- Reproduction Toxicity

Reproductive studies with certolizumab pegol have not been undertaken due to the lack of recognition of rodent TNF and immunogenicity in rats. Instead, the homologous agent cTN3 PF, which is a chimeric Fab' fragment conjugated to 40 kDa PEG, was tested in the reproductive and developmental toxicity studies. The IC_{90} for cTN3 PF against rat TNFα was approximately 15 nM and KD was 6.7 nM. Expected pharmacological activity was shown in an arthritis model in the mouse at 100 mg/kg, while 10 and 30 mg/kg had minimal or lacked effects.

A standard package of reproductive toxicity studies in the rat was submitted. Doses used were 20/30 and 100 mg/kg twice weekly. In male rats, reduced sperm motility and a trend of reduced sperm count were observed at both doses. Testis weight was increased in rats at 100 mg/kg. There were no effects on mating, or unexpected macro/microscopic findings. In female rat studies covering dosing throughout the complete reproductive cycle, there were no effects on fertility, reproductive function or developmental effects on offspring. Distribution studies have demonstrated that placental and milk transfer of cTN3 PF is negligible.

In addition, reproductive/developmental toxicity data for a full antibody which inhibits rodent TNF, cTN3 γ1, has been submitted. Administration of this compound resulted in some foetal exposure and exposure of offspring via milk. Overall, no effects on female fertility, reproductive function or embryo-foetal and postnatal development were observed. As male fertility and sperm parameters were not studied, this is requested as a clinical follow up measure.

Although these data provide some support for lack of reproductive and developmental toxicity with certolizumab pegol, they are insufficient for recommendations on the use in women of child-bearing potential and in pregnancy. These results and the unknown clinical relevance of these findings are adequately reflected in the Product Information (PI). A clinical evaluation of the effect of certolizumab pegol treatment on male sperm quality has been agreed as a follow-up measure.

- Toxicokinetic data

Toxicokinetic data from the 28 day cynomolgus monkey i.v. study, indicated that plasma concentrations of certolizumab pegol increased from the first to the fourth dosing cycles. The half-life ranged from 3 to 9 days, as determined during the recovery phase. Mean plasma concentrations (end of fourth infusion) in this study for the 50, 100 and 400 mg/kg groups were 1558, 2800 and 9825 µg/mL, respectively.

- Local tolerance

Local tolerance in rats was studied after a single dose of 200 mg s.c. of certolizumab pegol as a liquid or lyophilized formulation. Rats were observed for 29 days. There were no overt signs of toxicity or effects on the general health of the animals. On Day 2, slight swelling and erythema at the injection site were common but were not seen on Day 8 post-injection. Mild subcutaneous oedema was noted at necropsy on Day 2 in several groups. No gross findings were noted at 8, 15, and 29 days post-injection.

No local toxicity was seen when comparing certolizumab pegol second generation formulation (new liquid clinical formulation) with certolizumab pegol first generation (manufactured using the original process) in rats. Data from the repeat dose toxicity studies in monkeys, where the formulation intended for marketing was used, also support acceptable local tolerance. The finding of foamy macrophages at the injection site should be noted.

- Other toxicity studies

Antigenicity

No specific antigenicity studies have been conducted because antigenicity of a humanized Fab' in animals is not predictive of immunogenicity in man. Determinations of antibodies against certolizumab pegol have been performed in the general toxicity studies. The antibody incidence in the main monkey toxicity studies were 10-20%. It should be noted that the presence of CDP870 in the plasma sample interferes with the antibody analyses, and thus data are uncertain. Presence of antibodies resulted in shortened $t_{1/2}$. There were no apparent toxicological consequences of antibody formation.

Ecotoxicity/environmental risk assessment

A program to assess the environmental risk of certolizumab pegol has been conducted. In accordance with the Guideline on the Environmental Risk Assessment (EMEA/CHMP/SWP/4447/00), an estimate of the crude predicted environmental concentrations (PEC) of the active entity, certolizumab pegol, in the aquatic compartment was calculated. However, the nature of the product and subsequent metabolism indicates that such analysis is not appropriate for this product.

Certolizumab pegol is a humanised antibody Fab' fragment and as such can reasonable be expected to be subject to the same degradative pathways and to have the same environmental impact as naturally occurring human antibodies. It is unlikely that any pharmacologically active antibody enters the aquatic compartment. No adverse environmental impact is expected from excipients used in the finished product.

No other environmental concerns are apparent for certolizumab pegol drug product; certolizumab pegol is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.4 Clinical aspects

Introduction

Certolizumab pegol, in combination with MTX, is intended for the treatment of moderate to severe, active RA in adult patients when the response to DMARDs, including MTX, has been inadequate.

The clinical programme for certolizumab pegol included three 24-week Phase 3 studies and one 52-week Phase 3 study, and one Phase 2 dose-finding study. An overview of the clinical Phase 2 and Phase 3 programme with certolizumab pegol in RA is given in (Table 2). Long-term data were provided from a 104-week extension of this Phase 2 dose-ranging study and three open-label extension studies of the Phase 3 trials.

In the Phase 3studies CDP870-011, 014 and 027, a lyophilized formulation was used, while a liquid formulation, the proposed commercial form, was used in study CDP870-050. These studies were conducted in up to 30 countries across various geographic regions including the United States, Western Europe, Central and Southern America, Russian, Baltic States and Scandinavia and Eastern Europe.

Table 2   Overview of Phase 2 and Phase 3clinical studies with certolizumab pegol

Study ID/ Design	Study Posology Duration	Study Objective	Subjects by arm entered / completed	Primary Endpoint
Dose Finding (Phase 2)				
CDP870-002 Double blind, placebo-controlled, single ascending dose study, with optional open-label second dose	CZP[(b)] 1 mg/kg, 5 mg/kg, or 20 mg/kg or Placebo/ single dose i.v. 16 weeks	Efficacy and safety in RA; PK and immunogenicity	36 (Placebo: 12, 8 per arm); PP: 29 (5, 7, 8, 8)	Disease activity : ACR20, and ACR50; AEs
CDP870-004 Two-panel, placebo-controlled, parallel-group, dose-ranging study, with open-label extension	CZP[(b)] 50 mg, 100 mg, 200 mg, 400 mg or Placebo (Panel 1); CZP[(b)] 600 mg, 800 mg or Placebo (Panel 2) /q4w s.c. 12 weeks	Dose-finding study	Panel 1: 204 (Placebo: 40; active: 40-41/arm); Panel 2: 122 (Placebo 44, active: 39/arm). PP: 186, and 113 pts.	Efficacy of s.c. 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg CZP vs. placebo administered at 0, 4, and 8 weeks with assessments to 12 weeks. Efficacy was defined as a ACR20 improvement in disease activity at Week 12.
Phase 3 Placebo-Controlled				
CDP870-011 Double-blind, placebo-controlled, parallel-group study	CZP[(c)] 400 mg or Placebo/q4w s.c. 24 weeks	Efficacy of CZP 400 mg every 4 weeks to placebo (ACR20), safety and tolerability;	220 (Placebo: 109, active: 111), completed PP: 170 (81/89)	ACR20 (plus additional secondary efficacy criteria)
CDP870-014 Double-blind, placebo-controlled, parallel-group study	CZP[(c)] 400 mg or Placebo +MTX/q4w s.c. 24 weeks	Efficacy of CZP in combination MTX (ACR20), safety and tolerability sytemic exposure and immunogenicity	247 (Placebo: 121; active: 126); completed: 171 (Placebo: 79, active: 92)	ACR20 at Week 24
CDP870-027 Double-blind, placebo-controlled, parallel-group study	CZP[(c)] 400 mg, 200[(d)] mg or Placebo + MTX/q2w s.c. 52 weeks	Efficacy of 2 dose regimens of CZP in combination with MTX compared to MTX alone; RA activity and inhibition of progression of structural damage	982 (Placebo:19, 200 mg: 393, 400 mg: 390); completed PP: 572 (Placebo: 43; 200 mg: 393, 400 mg: 274)	ACR20 at Week 24 Change from baseline mTSS at Week 52
CDP870-050	CZP(e) 400 mg,	Efficacy of 2 dose	619 (placebo: 137;	ACR20 at Week 24

Study ID/ Design	Study Posology Duration	Study Objective	Subjects by arm entered / completed	Primary Endpoint
Double-blind, placebo-controlled, parallel-group study	200(d) mg or Placebo + MTX/q2w s.c. 24 weeks	regimens of a liquid formulation of CZP in combination with MTX to MTX alone; safety and tolerability, PK	200 mg: 246, 400 mg: 246); completed PP: 594 (placebo: 125, 200 mg: 231, 400 ,g 238)	

GCP

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

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

Pharmacokinetics

The clinical pharmacokinetics development programs of certolizumab pegol (CZP) includes four healthy volunteer studies (CDP870-001, CDP870 003, PHA-024 and CDP870-038), and one study of the pharmacokinetics (PK) of certolizumab pegol in subjects with RA receiving methotrexate (MTX) (PHA-001).

The full pharmacokinetic profile of certolizumab pegol has only been characterised after single dose administration in healthy subjects. There are, however, a large number of sparse sampling data from the pivotal clinical studies that have been used, together with the data from intensive sampling schedule in the healthy volunteer studies, in a population pharmacokinetic analysis. This analysis contributes to the pharmacokinetic documentation, including estimations of pharmacokinetic parameters, evaluating special populations and interactions. The population PK model has been shown to have reasonable predictive properties and supports the current usage of the model.

A sandwich ELISA was used to determine the concentration of certolizumab pegol in plasma. This assay was validated for use in human plasma and this included a supplementary report on the stability of certolizumab pegol in human plasma at -20°C and -70°C for up to 2 years. The limit of quantification (LOQ) was 4.1 ng/ml.

Anti-CZP antibodies were determined in plasma using a similar validated ELISA. The limit of quantification for the assay is 0.06 µg/ml. Allowing for a sample dilution of 1/10, the LOQ for samples is 0.6 units/ml where one unit is equivalent to 1 µg of the rabbit calibrator.

Residual certolizumab pegol in plasma samples will interfere in this assay. Data from Study CDP870-004 (the study with the largest amount of data available for evaluation at the end of Phase 2) in subjects with RA were used to set a baseline for the screening ELISA so that a positive antibody response could be defined. The baseline was set at twice the mean of pre-infusion values from all subjects entering CDP870-004. Subject plasma samples were considered positive for antibodies to CZP if they showed a greater than two-fold increase over this baseline. This resulted in a definition of an antibody positive subject being one in which the anti-CZP antibody concentration exceeded 2.4 units/ml at any time point. This definition was retained for subsequent studies for consistency.

Non-compartmental methods were used to estimated the following PK parameters: C_{max}, t_{max}, AUC_t, AUC_{inf}, z, $t_{1/2}$, V_z, CL and MRT. Pharmacokinetic parameters were tabulated by treatment groups and with descriptive statistics. The pharmacokinetic parameters C_{max} and AUC were dose adjusted (C_{max}_Dn) and AUC_Dn, respectively) to a dose of 1 mg/kg and summarized using descriptive statistics.

- Absorption

Bioavailability

The bioavailabilty of certolizumab pegol was determined in study CDP870-003, a single ascending dose study in healthy male subjects comparing s.c. with i.v. dosing. An ascending dosage group design was employed at dosage levels of 20 mg, 60 mg and 200 mg administered subcutaneously compared with intravenous infusion of 1 mg/kg certolizumab pegol administered over 60 minutes. Subjects were assessed over an 8-week period following dosing. Following completion of the treatment described above, an additional, open-label treatment group of 6 subjects was added to the study. This group received an s.c. injection of 20 mg certolizumab pegol, diluted to a total volume of 1.0 ml with saline to assess the pharmacokinetics and immunogenicity of a 20 mg/ml dose solution. Blood samples were collected for the analysis of certolizumab pegol plasma concentrations pre-dose; 30, 60, 75 and 90 minutes post start of infusion (or s.c. injection for second part of the study); and at 2, 3.5, 6, 12, 18, 24 and 36 hours, and on Days 2, 2.5, 3, 4, 5, 6, 7, 10, 14, 21, 28, 42 and 56 post dose.

The results of study CDP870-003 are presented in Table 3.

Table 3 PK Results of single ascending-dose study of certolizumab pegol in healthy male subjects comparing s.c. with i.v. dosing (Study CDP870-003)

Dose	C_{max} (µg/ml)	T_{max} (h)	AUC (µg*h/ml)	$t_{1/2z}$ (days)[a]	CL (ml/h)	FAUC (%)
1 mg/kg i.v.	32.62	1.92	8,208	12.02	10.46	N/A
20 mg s.c. in 0.1 ml	2.68	103	NC	NC	NC	NC
20 mg s.c. in 1 ml	2.45	72	1,788	18.48	12.13	81
60 mg s.c. in 0.3 ml	10.98	54	5,856	11.83	10.58	88
200 mg s.c. in 1 ml	30.98	84	16,776	12.53	12.13	76

Geometric mean values are presented for each variable except T_{max}, which is expressed as a median
NC=Not calculated, N/A=Not applicable
[a] Units have been converted from clinical study report for consistency across the Clinical Pharmacology Summary
FAUC = bioavailability based upon AUC values (AUC sc/AUC iv), dose adjusted

The bioavailability of certolizumab pegol 200 mg/ml formulation was 81%, 88% and 76% following s.c. administration of 20 mg, 60 mg and 200 mg, respectively. Following subcutaneous injection, certolizumab pegol is slowly absorbed and reaches maximum concentrations on average after about 2-7 days.

Bioequivalence

Study CDP870-038, a bioequivalence study with parallel group design, compared the lyophilized formulation used in many of the later-stage clinical studies and the optimized liquid formulation intended for marketing. The parallel design was chosen due to the risk of antibody formation from one treatment period to the next. Formal bioequivalence was not shown, as seen in Table 4 below. However, the difference in bioavailability seen was not large and is considered not to be of clinical significance.

Table 4 Inferential analysis on PK parameters of certolizumab pegol after single s.c. administration of 400 mg lyophilized formulation (reference) and liquid formulation (test)

Parameters	CZP 400 mg Lyophilized Formulation[a]	CZP 400 mg Liquid Formulation[a]	CV[b] (%)	Test versus Reference[c] Point estimate	90% CI
C_{max} (µg/mL) (N=48)	63.48 (54.74-73.61)	57.99 (50.00-67.24)	36.0	91.35	(76.71-108.8)
$AUC_{(0-t)}$	1355 (1184-1551)	1178 (1029-1349)	32.9	86.97	(74.15-102.0)

(µg.d/mL) (N=48)					
AUC (µg.d/mL) (N=48)	1392 (1218-1592)	1209 (1057-1382)	32.6	86.82	(74.13-101.7)
t_{max} (d) (N=48)	5.50 (3.00-21.00)	5.00 (3.00-14.00)	NA	-0.001	(-1.000-0.000)

AUC=area under the plasma concentration time curve; AUC$_{(0-t)}$=area under the plasma concentration time curve from time zero to last measurable concentration; CI=confidence interval; C$_{max}$=maximum observed plasma concentration; CV=coefficient of variation; CZP=certolizumab pegol; d=day; N=number of subjects; NA=not applicable; t_{max}=time to maximum plasma concentration

(a) Values are least square geometric means (95% confidence interval), t_{max} values are median (minimum-maximum)

(b) Inter-subject coefficient of variation (%)

(c) Point estimate (90% CI) for the test/reference geometric least square means ratio derived from ANOVA; for t_{max}: median point estimate (90% non-parametric CI) of the difference test-reference

- Distribution

The apparent volume of distribution (V/F) was estimated to be 8.01 l in the population PK analysis for subjects with RA with an inter-subject variability of 30.9% CV.

- Elimination

Elimination pathways and metabolism mediated interactions have not been studied since these areas generally are considered predictable for protein drugs. Only limited human data are currently available on the pharmacokinetics of PEG. The de-conjugated PEG component is rapidly eliminated from plasma and is to an unknown extent excreted renally.

In human pharmacokinetic studies in healthy volunteers certolizumab pegol plasma clearance (CL/F; total body clearance divided by fraction of the dose absorbed) was estimated by taking the ratio between the dose administered and the AUC extrapolated to infinity. In Study CDP870-001, during which certolizumab pegol was administered i.v., mean clearance values ranged from 9.21 ml/h to 14.38 ml/h. In Study CDP870-003, clearance was estimated to be 10.46 ml/h following i.v. dosing and ranged from 10.58 ml/h to 12.13 ml/h following s.c. dosing (Table 3).

The population PK analysis of data from subjects with RA resulted in an estimated clearance of 21.04 ml/h (0.505 l/day) for a 71.5 kg anti-certolizumab pegol antibody negative patient in the final model for the overall population, with an inter-subject variability of 30.8% (CV) and an inter-occasion variability of 22.0%. Certolizumab pegol has a long elimination half-life (t$_{1/2}$) of approximately 14 days.

The presence of antibodies to certolizumab pegol resulted in an approximately three-fold increase in clearance.

- Dose proportionality and time dependencies

Certolizumab pegol exhibits roughly dose-linear pharmacokinetics. The average plasma concentrations are similar over 24 weeks suggesting time-independent pharmacokinetics. For the antibody positive patients a time dependent decrease in exposure was evident.

- Special populations

Population pharmacokinetics was used to characterize the pharmacokinetics of certolizumab pegol in the RA patient population, including estimation of inter-subject variability in the main pharmacokinetic parameters and identification of important demographic and physiologic determinants of certolizumab pegol. The data set used for population PK analyses consisted of six studies (Studies CDP870-004, CDP870-011, CDP870-014, CDP870-027, CDP870-050 and PHA 001).

The population analysis did not indicate a strong impact of **gender** on the pharmacokinetics of certolizumab pegol. Further, an effect of **age** was not identified in the population analysis in a material including patients up to 83 years of age (13% above 65 years). An effect of **weight** on the pharmacokinetics of certolizumab pegol was identified in the population PK analysis; however, there was no indication of a lower efficacy in individuals with large body weights in the clinical sub-group analysis.

Certolizumab pegol has not been studied in **children** and is not proposed to be indicated for children.

The impact of race on the pharmacokinetics certolizumab pegol was not evaluable due to the small number of subjects in each group other than Caucasians. However, clinically relevant differences between various **ethnicities** are not expected. The difference in pharmacokinetic parameters between the Japanese and the Caucasian population was specifically studied in a bioavailability study, in which single s.c. doses of certolizumab pegol 100, 400 and 800 mg were given to healthy Japanese and Caucasian subjects. Only a small difference was seen which was not considered clinically relevant.

The effect of moderate to severe **renal or hepatic impairment** has not been studied in separate pharmacokinetic studies. Thus, the pharmacokinetics and safety of certolizumab pegol in patients with moderate to severe renal or hepatic impairment are not known. However, since certolizumab is not expected to be extensively eliminated through hepatic routes, the lack of information regarding hepatic impairment is acceptable. Although the certolizumab pegol complex is too large to be eliminated through renal routes, the PEG fraction could possibly be renally excreted to a large extent. Therefore, the information is at present considered insufficient to provide dosing recommendation in moderate and severe renal impairment, which is stated in the SPC section 4.2.

- Pharmacokinetic interaction studies

In vitro cytochrome P450 inhibition studies with human microsomes were not performed because proteins and immunoglobulin antibodies do not compete for the cytochrome P450 metabolism system. P-glycoprotein mediated transport of digoxin and vinblastine were investigated in both Caco-2 and MDCK+PGY1 cell monolayer systems. It was shown that neither certolizumab pegol nor its non-pegylated Fab' fraction were inhibitors of p-glycoprotein mediated transport.
Formal drug-drug interaction studies *in vivo* have not been performed other than the potential for a PK drug-drug interaction between MTX and certolizumab pegol which was examined in subjects with RA (PHA-001). In this study a small effect on MTX in the presence of certolizumab pegol was demonstrated that is not considered clinically relevant. Furthermore, the population PK analysis in subjects with RA indicated that concomitant administration with MTX, corticosteroids, NSAIDs and analgesics had no effect on the pharmacokinetics of certolizumab pegol.

Immunogenicity
The presence of antibodies to certolizumab pegol was assessed in all clinical studies except the MTX interaction study in subjects with RA (PHA-001).

In the Phase 3 placebo controlled studies of RA where subjects received 400 mg s.c. the incidence of subjects testing positive for antibodies was 22.5% in study CDP870-011, and considerably lower in studies CDP870-014, CDP870-027 and CDP870-050 where MTX was co-administered, namely 4.0% (400 mg q4w), 10.7% (200 mg q2w) and 8.5% (200 mg q2w), respectively. The fraction of patients developing antibodies had generally increased at the safety follow up. It is important to note that the detection of anti-CZP antibodies can be hampered by the presence of certolizumab pegol in the plasma, which may lead to false negative results and therefore to an underestimation of the incidence of antibody generation. Further, the definition of an anti-CZP antibody positive subject is also dependent on the value used as cut-off in the definition. The applicant has presented a time-to-event model describing the incidence of antibody response during the 6- to 12- month observation period with predictions being in reasonable agreement with the observed data. The occurrence of antibodies has been shown to result in an increase in certolizumab pegol clearance of approximately three-fold. The markedly higher clearance in antibody positive subjects was indicated to result in reduced clinical

efficacy and the predictions made on the basis of the exposure-response model also point in the same direction.

An ELISA analysis of human plasma samples positive for antibodies to infliximab did not suggest that anti-infliximab antibodies bound certolizumab pegol. Human plasma samples positive for anti-CDP870 antibodies did not cross react with infliximab, etanercept or adalimumab. There are data available to confirm that antibodies were neutralising, but these data are insufficient to assess the possibility for cross-reactivity with other anti-TNF antibodies.

- Pharmacokinetics using human biomaterials

No *in vitro* pharmacokinetic studies involving human biomaterials were conducted.

Pharmacodynamics

- Mechanism of action

Certolizumab pegol has a high affinity for human TNFα and binds with a dissociation constant (KD) of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα but does not neutralize lymphotoxin α (TNFβ). Certolizumab pegol was shown to neutralize membrane associated and soluble human TNFα in a dose dependent manner. Incubation of monocytes with Certolizumab pegol resulted in a dose dependent inhibition of LPS-induced TNFα and IL-1β production in human monocytes.

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes, or neutrophil degranulation.

- Primary and Secondary pharmacology

There is only non-clinical support for certolizumab pegol being a selective anti-TNF agent. Specific PD markers were not assessed within the clinical trials.

Clinical efficacy

- Dose response study

Study CDP870-004 was a double-blind, multiple dose, 2-week, placebo-controlled dose-ranging study to compare efficacy and safety of certolizumab pegol and placebo in 326 subjects with a history of inadequate response or intolerance to at least one DMARD and active RA at screening. DMARD therapy was discontinued at least one month prior to study start; concomitant NSAID and ≤ 10 mg prednisone or equivalent/day were allowed. Patients received 50, 100, 200, 400, 600 and 800 mg s.c. q4w in two dose groups, panel 1 and panel 2.

The primary measure of efficacy was ACR20 Responder Rates at Week 12 (Table 5). A number of secondary efficacy measures were also included, e.g. ACR20 at all available visits except Week 12, ACR50, ACR70, subset of the ACR criterion, DAS.

Table 5   Overview ACR20 responder rates in study CDP870-004.

Treatment	Panel 1					Panel 2		
	Placebo	CDP-870 50 mg	CDP-870 100 mg	CDP-870 200 mg	CDP-870 400 mg	Placebo	CDP-870 600 mg	CDP-870 800 mg
N	40	39	40	41	42	44	39	38
Week 1	3	31*	23*	44*†	45*†	9	49*	53*
Week 4	15	31	28	51*†	48*	12	59*	74*
Week 8	13	23	40*	39*	64*‡	19	67*	66*
Week 12	15	21	20	34	60*‡	19	64*	79*

* p< 0.05 versus placebo within the panel (Cochran-Mantel-Haenszel test controlling for country); ‡ p<0.05 versus CDP-870 50, 100 and 200 mg; † p <0.05 versus CDP-870 100 mg.

For the stricter ACR50 and ACR70 criteria, statistically significant results were seen in the 400 mg dose group; for 200 mg ACR50 differed significantly as well. There was no clear difference between 400, 600 and 800 mg with respect to percentage of ACR50/70 responders.

Based on these data, the applicant selected 400 mg every fourth week (q4w) for two Phase 3 studies, CDP870-011 and 014. After completion of study 014, additional PK modeling suggested that more frequent dosing (200 mg q2w) would increase the C_{trough} and potentially improve the clinical response. Therefore, subsequent Phase 3 studies tested 200 and 400 mg every second week (q2w).

- Main studies

The design of the four Phase 3 studies was largely similar; however, only two studies (CDP870-027 and CDP870-050) evaluated certolizumab pegol in its proposed posology of 200 mg q2w in combination with oral methotrexate (MTX) and were therefore considered pivotal. A summary of the major design and methodological characteristics common across all four Phase 3 trials is given below.

METHODS

Study participants
The key inclusion criteria included:
- ≥ 18 years of age
- Active RA of at least 6 months duration as defined by:
  - ≥9 tender joints; and
  - ≥9 swollen joints; and
  - ≥30 mm/hour ESR or CRP >15 mg/l (studies 027 and 050); ≥45 minutes of morning stiffness or ≥28 mm/hour ESR or CRP >10 mg/l (studies 011 and 014)

- Studies 027, 050 and 011: Treatment with MTX (with or without folic acid) for at least 6 months prior to the baseline visit, with stable dose at least 2 months before baseline visit. The minimum MTX dose was 10 mg weekly (studies 027, 050) or 15 mg weekly (study 014).
- Study 014: Discontinue all DMARD at least 28 days or five half-lives, whatever longer, prior to first dose of study drug

The inclusion criteria in the add-on studies were largely similar to those used in previous studies with anti-TNF agents in support of a second line indication in RA, although monotherapy in subjects with inadequate response to DMARD has not been studied with all anti-TNFs.
Exclusion criteria included identified contraindications for anti-TNF agents, and were considered relevant.

Treatments
In studies 027 and 050, placebo was compared with 200 mg or 400 mg certolizumab pegol every 2 weeks (q2w) as add-on therapy to oral MTX. Subjects randomized to the 200 mg q2w treatment group received three loading doses of 400 mg administered at Weeks 0, 2, and 4 in order to ensure rapid initial rise in plasma certolizumab pegol concentration. The study duration was 24 weeks (050) or 52 weeks (027), respectively.

The majority of patients included in the studies received MTX (in studies CDP870-014, -027, and -050), while in study CDP870-011 RA patients, being refractory or intolerant to at least one DMARD, were treated without concomitant DMARD therapy (i.e. certolizumab pegol monotherapy).

Early escape: In studies 027 and 050, patients who failed to achieve an ACR20 response at Week 12, confirmed at Week 14, were designated as treatment failures. After the Week 14 visit, these patients were withdrawn and offered the choice of entering an open-label extension study at Week 16.

For details about the dose regimens and treatments in each study refer to Table 2.

Objectives
In all pivotal studies the primary study objective was to assess the efficacy and safety of certolizumab pegol either compared to placebo (alone) or together with MTX. Efficacy was assessed primarily by ACR improvement criteria. Safety was assessed in every study, also in comparison with certolizumab pegol systemic exposure. In one study (CDP870-027) the effects of certolizumab pegol on the reduction of the rate of progression of structural joint damage as measured by X-ray were also assessed.. In all studies, PK parameters were measured in selected patients either to assess bioequivalence of different formulations or to collect population PK data.

Outcomes/endpoints
In all four studies, the primary endpoint was ACR20 response at Week 24, addressing signs and symptoms of disease. Study 027 had a co-primary endpoint of change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Week 52, for evaluation of structural damage.

Secondary endpoints included ACR50/70 responses, major clinical response, subsets of the ACR components, HAQ-DI and SF–36 addressing physical function and disability, as well as endpoints addressing tiredness, productivity. Some additional efficacy measures such as DAS28, DAS remission were also studied.

Further detail on main endpoints:

Signs & symptoms endpoints
• American College of Rheumatology (ACR) 20/50/70 response: the assessments were based on a ≥20/50/70% improvement from baseline in the number of both tender joints and swollen joints, and in 3 of the 5 core set measures:
    - Patient's Assessment of Arthritis Pain (measured by VAS)
    - Patient's Global Assessments of Disease Activity (measured by VAS)
    - Physician's Global Assessments of Disease Activity (measured by VAS)
    - physical function based on the HAQ-DI
    - C-reactive protein (CRP)
• Assessment of joint tenderness and swelling: A total of 68 joints were examined for tenderness, including joints in the upper body, upper extremity, and lower extremity. An assessment for swelling was made on 66 joints of the 68 joints evaluated for tenderness; the hip joints were excluded. Swelling and tenderness were graded on a 4-point scale.

Reduction of the rate of the progression of structural joint damage
Radiographs of the hands and feet were taken to assess disease progression. A single posterioanterior view of each hand and a single dorsoplantar image of each foot were taken prior to first dose of investigational product at Baseline and at Weeks 24 and 52/Withdrawal visit.

The degree of joint damage was assessed using the van der Heijde **modified Total Sharp Score (mTSS)**. This methodology quantifies the extent of bone erosions and joint space narrowing for 44 and 42 joints, respectively, with higher scores representing greater damage. Each radiograph was read centrally and independently by 2 of 3 experienced readers who were blinded for treatment, visit, and patient identification. The mean score of the readers was used for analysis.

Randomisation
Eligible patients were randomized through an Interactive Voice Response System (IVRS) to receive 1 of 2 dosing regimens of certolizumab pegol or placebo in a 2:2:1 ratio. The randomization code was generated by an independent group following instruction of the randomization procedures prepared by the Project Statistician. Randomization was centralized via IVRS and access information was supplied.

Blinding
All sponsor, investigator sites and CRO staff involved with the study were blinded to the treatment code, except Sponsor Clinical Trials Supplies Coordinator or qualified person, Site pharmacy staff involved in investigational product storage and preparation, unblinded CRO monitors that only monitored for the investigational product accountability, Sponsor pharmacovigilance staff reporting SAEs to regulatory authorities, unblinded staff that performed ESR testing.

In addition, due to the difference in viscosity between the placebo and certolizumab pegol solutions, the injections were administered by an Investigator-delegated individual whose only other involvement in study conduct could be performing ESR testing. Blinding was also maintained by not disseminating PK sample or CRP results to sites during the study. Standard procedures for unblinding in case of a medical emergency were in place.

Statistical methods
The intent-to-treat (ITT) population consisted of all randomized patients. In the case of dosing administration error, analyses on the ITT population were conducted according to randomized treatment. This was the primary efficacy population. The per-protocol (PP) populations were a subset of the ITT population, consisting of those patients who had no major protocol deviations affecting either primary efficacy variable or relating to the integrity of the study conduct, as confirmed during a pre-analysis review prior to unblinding of the data.

Post-baseline deviations did not necessarily lead to exclusion of a patient from PP analyses but may have led to exclusion of data. The date from which a patient was excluded was confirmed during the pre-analysis meeting, in addition to the classification of patients to patient populations. These PP populations were used for sensitivity analyses on the primary endpoints only and for summary statistics of the demographic characteristics at Baseline. The two PP populations were PP (signs and symptoms) and PP (structural damage).

The safety population consisted of all patients who received at least one injection of investigational product. In the case of dosing administration error, analyses on the Safety Population were conducted according to actual treatment received.

In the following, the design and results of the two pivotal studies (CDP870-027 and -050) are presented/described in more detail. Where appropriate, an overview of results from all four Phase 3 studies is given.

Participant flow in study CDP9870-027:

```
                          ┌─────────────────┐            ┌──────────────────┐
                          │    Screened     │───────────▶│  Screen Failures │
                          │    (n=1262)     │            │     (n=280)      │
                          └─────────────────┘            └──────────────────┘
                                   │
                          ┌──────────────────────────┐
                          │ Randomised: n=982ᵃ        │
                          │ ITT population: n=982     │
                          │ Safety population: n=980  │
                          └──────────────────────────┘
                                   │
        ┌──────────────────────────┼──────────────────────────┐
        │                          │                          │
┌───────────────────┐   ┌───────────────────────┐   ┌───────────────────────┐
│ Placebo:          │   │ CZP 200 mg:           │   │ CZP 400 mg:           │
│ ITT: n=199 (100%) │   │ ITT: n=393 (100%)     │   │ ITT: n=390 (100%)     │
│ Safety: n=199     │   │ Safety: n=392ᵇ(99.7%) │   │ Safety: n=389ᶜ(99.7%) │
│        (100%)     │   │                       │   │                       │
└───────────────────┘   └───────────────────────┘   └───────────────────────┘
        │                          │                          │
┌───────────────────┐   ┌───────────────────────┐   ┌───────────────────────┐
│ Completed:        │   │ Completed:            │   │ Completed:            │
│ n=43 (21.6%)      │   │ n=255 (64.9%)         │   │ n=274 (70.3%)         │
├───────────────────┤   ├───────────────────────┤   ├───────────────────────┤
│ Withdrawn:        │   │ Withdrawn:            │   │ Withdrawn:            │
│ n=156 (78.4%)     │   │ n=138 (35.1%)         │   │ n=116 (39.7%)         │
└───────────────────┘   └───────────────────────┘   └───────────────────────┘
        │                          │                          │
┌───────────────────┐   ┌───────────────────────┐   ┌───────────────────────┐
│ Withdrawn at Week │   │ Withdrawn at Week     │   │ Withdrawn at Week     │
│ 16 due to Lack of │   │ 16 due to Lack of     │   │ 16 due to Lack of     │
│ Efficacy:         │   │ Efficacy:             │   │ Efficacy:             │
│ n=125 (62.8%)     │   │ n=83 (21.1%)          │   │ n=68 (17.4%)          │
└───────────────────┘   └───────────────────────┘   └───────────────────────┘
```
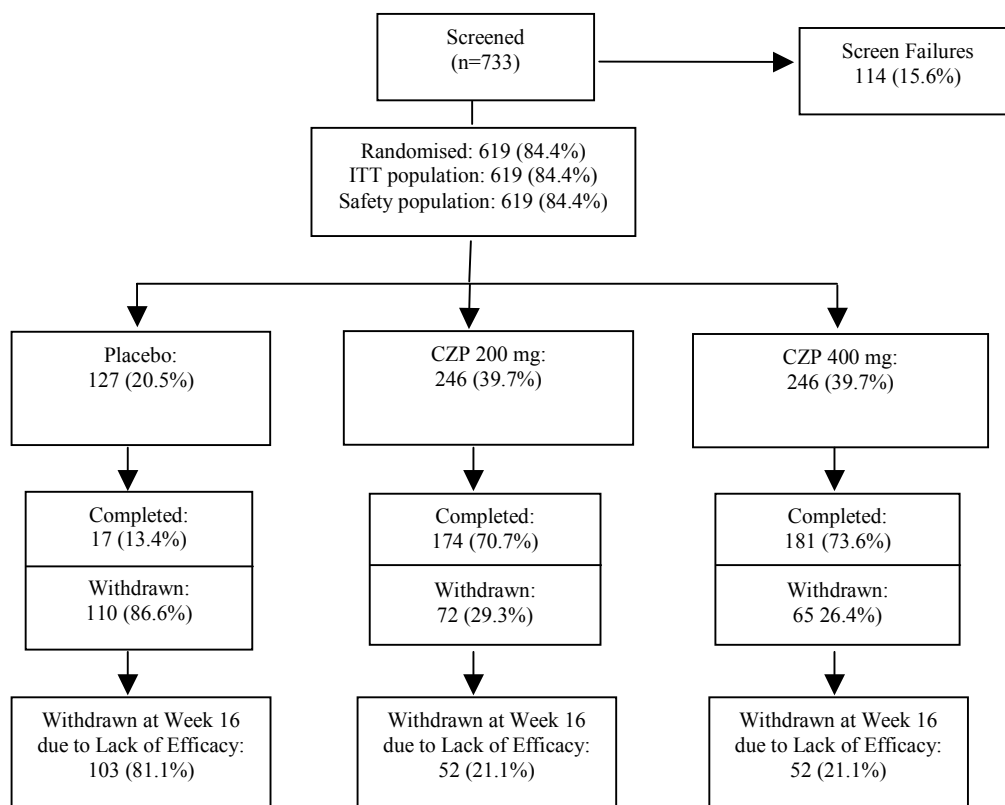
a Excluding 10 patients removed from the analysis due to GCP inspection findings;
b One patient withdrew by her own decision;
c One patient was discontinued due to the ESR/CRP not meeting entry criteria.

Participant flow in study CDP9870-050:

```
                    ┌─────────────────┐
                    │    Screened     │ ─────────────→  ┌──────────────────┐
                    │    (n=733)      │                 │  Screen Failures  │
                    └─────────────────┘                 │   114 (15.6%)     │
                            │                           └──────────────────┘
                ┌───────────────────────────────┐
                │ Randomised: 619 (84.4%)        │
                │ ITT population: 619 (84.4%)    │
                │ Safety population: 619 (84.4%) │
                └───────────────────────────────┘
```

Placebo: 127 (20.5%)	CZP 200 mg: 246 (39.7%)	CZP 400 mg: 246 (39.7%)
Completed: 17 (13.4%)	Completed: 174 (70.7%)	Completed: 181 (73.6%)
Withdrawn: 110 (86.6%)	Withdrawn: 72 (29.3%)	Withdrawn: 65 26.4%)
Withdrawn at Week 16 due to Lack of Efficacy: 103 (81.1%)	Withdrawn at Week 16 due to Lack of Efficacy: 52 (21.1%)	Withdrawn at Week 16 due to Lack of Efficacy: 52 (21.1%)

Recruitment

The earliest Phase 3 study started in 2002 completed in 2004, the latest ones in 2005. One was completed in January 2004; the others in July 2004, and September 2006. The extension studies are still ongoing.

Conduct of the study

Minor amendments were made in some studies, either not affecting outcomes or statistical analysis or in order to make studies uniform.

One investigator in study 027 (also site in 028, 050 and 051) was banned from further participation following a routine GCP inspection by the national authority. Subsequently, 10 patients treated at this site discontinued treatment and the data from these patients were excluded from the analysis.

Baseline data

The general demographic and disease characteristics of patients in Phase 3 studies (ITT population) are summarized in Table 6 below.

Table 6 Demographic and Disease Characteristics of the Phase 3 Studies[a]

Study	CDP870-011 N=220	CDP870-014 N=247	CDP870-027 N=982	CDP870-050 N=619
Age (years) Mean (SD)	53.8 (12.2)	54.3 (12.05)	52.0 (11.6)	51.9 (11.5)
Female (%)	83.6%	69.2%	83.2%	81.6%
Disease Duration (years) Mean (SD)	9.5 (NC)	9.6 (NC)	6.1 (4.3)	6.2 (4.2)
RF-positive [≥ 14 IU/ml] (%)	100%	78%	81.8%	76.9%
MTX dose (mg/week) Mean	N/A	16.8	13.6	12.5
Number of Previous DMARDS (Mean)	2.0	1.3	1.3	1.2
Tender Joint Count Mean (SD)	29.0 (13.13)	30.0 (12.28)	30.7 (12.9)	30.2 (14.0)
Swollen Joint Count Mean (SD)	20.5 (9.67)	22.5 (9.48)	21.5 (9.8)	21.0 (9.8)
HAQ-DI mean (SD)	1.5 (0.64)	1.4 (0.63)	1.7 (0.60)	1.6 (0.59)
CRP (mg/l) Geometric Mean (CV)	11.5 (ND)	12.4 (NC)	14.7 (144.2)	13.6 (180.9)
DAS28(ESR) Mean (SD)	6.3 (1.00)	6.2 (0.99)	6.9 (0.8)	6.8 (0.83)

Notes: CV = coefficient of variation; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IU = international units; L = liter; mg = milligrams; mL = milliliters; RF= rheumatoid factor; SD = standard deviation; y = years; NC= not calculated; N/A=not applicable
[a] All randomized subjects; the actual numbers vary slightly across parameters

Numbers analysed
The number of patients in the four Phase 3 studies analyzed per arms is shown below.

Table 7 Intent-to-treat (ITT) and per protocol (PP) populations

Study Nr.	Placebo		200 mg CZP		400 mg CZP		Total	
	ITT	PP	ITT	PP	ITT	PP	ITT	PP
CDP870-011	109	81	N/A	N/A	111	89	220	170
CDP870-014	119	79	N/A	N/A	124	92	243	171
CDP870-027	199	43	393	274	390	255	982	572
CDP870-050	127	17	246	172	246	181	619	370

In studies 027 and 050, the number of withdrawals was high in the placebo groups, possibly due to the early escape option at Week 16. Table 4 shows the numbers who completed the respective studies.

Outcomes and estimation

Signs and symptoms
The outcome of the signs and symptoms endpoints for the two pivotal studies is presented below:

Table 8 ACR responses rates at Week 24 in studies CDP870-027 and 050

	CDP870-027			CDP870-050		
	Pbo + MTX (N=199)	200 mg + MTX (N=393)	400 mg + MTX(N=390)	Pbo+MTX (N=127)	200 mg + MTX (N=246)	400 mg + MTX (N=246)
N	198	388	388	127	246	245
ACR 20						
Responder (%)	27 (**13.6%**)	228 (**58.8%**)	236 (**60.8%**)	11 (**8.7%**)	141 (**57.3%**)	141 (**57.6%**)
Odds ratio (95% CI) [a] P-value [b]		9.2 (5.9, 14.6) <0.001	10.1 (6.4, 15.9) <0.001		14.4 (7.4, 28.2) <0.001	14.3 (7.3, 28.0) <0.001
ACR50						
Responder (%)	15 (**7.6%**)	144 (**37.1%**)	155 (**39.9%**)	4 (**3.1%**)	80 (**32.5%**)	81 (**33.1%**)
Odds ratio (95% CI) [a] P-value [b]		7.6 (4.3, 13.4) <0.001	8.5 (4.8, 15.1) <0.001		14.8 (5.3, 41.6) <0.001	15.3 (5.5, 42.9) <0.001
ACR70						
Responder (%)	6 (**3.0%**)	83 (**21.4%**)	80 (**20.6%**)	1 (**0.8%**)	39 (**15.9%**)	26 (**10.6%**)
Odds ratio (95% CI) [a] P-value [b]		9.2 (3.9, 21.7) <0.001	8.7 (3.7, 20.5) <0.001		23.8 (3.2, 176) ≤0.01	15.5 (2.1, 115) ≤0.01

(a) Odds ratio was calculated using logistic regression with factors for treatment and geographic region. (b) P-values for the comparison of treatment groups were calculated using logistic regression with factors for treatment and geographic region.

Table 9   ACR response rates at Week 52 in study CDP870-027

	CDP870-027		
	Pbo + MTX (N=199)	200 mg + MTX (N=393)	400 mg + MTX (N=390)
N	198	392	388
ACR20			
Responder (%)	26 (**13.1%**)	208 (**53.1%**)	213 (**54.9%**)
Odds ratio, (95% CI) (a), P-value (b)		7.7 [4.9, 12.2] <0.001	8.3 [5.2, 13.1] <0.001
ACR50			
Responder (%)	15 (**7.6%**)	149 (**38.0%**)	155 (**39.9%**)
Odds ratio, (95% CI) (a), P-value (b)		7.7 [4.3, 13.5] <0.001	8.3 [4.7, 14.6] <0.001
ACR70			
Responder (%)	7 (**3.5%**)	83 (**21.2%**)	90 (**23.2%**)
Odds ratio, (95% CI) (a), P-value (b)		7.6 [3.4, 16.8] <0.001	8.5 [3.8, 18.7] <0.001

For the primary endpoint, ACR20 at Week 24, a statistically significant and clinically relevant effect on signs and symptoms was shown for both dose levels of certolizumab pegol in combination with MTX (see Table 8). Consistent results were demonstrated in alternative sensitivity analyses.

Also secondary endpoints addressing signs and symptoms, physical function and other, e.g. quality of life related measures, showed statistically significant, and clinically relevant better efficacy with certolizumab pegol as add-on to MTX, compared with placebo + MTX.

In study 027, 52 week data were also obtained (Table 9). For both doses, the response rate dropped slightly (5-6%) for ACR20 at Week 52 vs. Week 24, while there was no difference for ACR50 and ACR70. Data from the open label extension of up to 2 years show some further reduction but overall, these data support maintained effect on signs and symptoms during the 2 years period.

Structural damage
The results of the primary analyses of X-ray data in study 027 are given in Table 10. Statistically significant and clinically promising results have been demonstrated up to 52 weeks. The findings have been found robust in appropriate sensitivity analyses, including a retrieved drop-out (RDO) analysis. All changes on active treatment, positive as well as negative, appear to be due to measurement error (Figure 1). Thus, the results are consistent with a complete inhibition of structural damage.

Table 10   Primary results on structural damage at 52 weeks in Study 027.

	Placebo + MTX	CDP870 200 mg + MTX	CPD870 400 mg + MTX
Change in mTSS from baseline to W52			
N	181	364	363
Mean (SD)	2.8 (7.8)	0.4 (5.7)	0.0 (4.8)
Median	0.0	0.0	0.0
P-value vs placebo		<0.001	<0.001
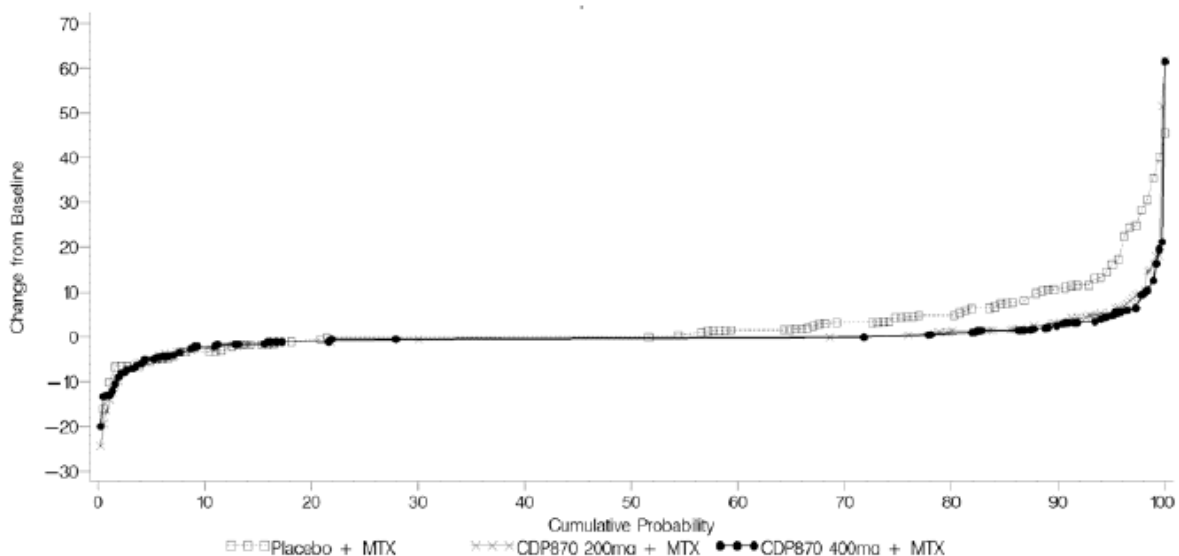
Figure 1   ***Cumulative Probability Plot of the Change from Baseline in mTSS at Week 52 – Linear Extrapolation – ITT Population***

During the review process, the applicant submitted additional X-ray data from study 028, the open label extension of study 027, obtained at two years. A number of descriptive analyses were presented. The results are indicative of a sustained inhibition of structural damage, but a number of deficiencies limit its value as conclusive evidence. With the separation into completers, withdrawers and switchers the possible comparisons are non-randomised, the possibility to switch already after 16 weeks leaves only 41 patients with one-year data on placebo, and the validity of the linear extrapolation is not immediately transparent.

To further substantiate the evidence of a sustained effect on progression of structural damage the applicant presented estimates of the percentage of patients with no progression (mTSS ≤ 0). In an analysis with linear extrapolation for patients missing X-ray data at two years, 63% [95% CI: 59.1; 66.9] had no progression on certolizumab treatment. In an ITT analyses including all patients initially randomised to certolizumab and counting patients without a two-year X-ray examination as failures, the percentage of patients with no progression was 47% [43.4; 50.6]. This is not far from the expected percentage in case of complete inhibition of structural damage, which should be close to 50% (all changes due to measurement error and a low percentage with mTSS=0). In certolizumab patients with X-ray data at one and two years the percentage of no progression during the second year was 69% [65.2; 72.8].

Patients pre-maturely withdrawn from treatment during the first year of the pivotal study (027) were retrieved for an X-ray examination at 52 weeks, irrespective of treatment after the withdrawal (no treatment, switched to open label certolizumab treatment, active treatment outside the study). One year X-ray data were obtained for 80%, 84% and 86% of the patients initially randomised to placebo, certolizomab 200 mg or 400 mg, respectively. In a sensitivity, truly conservative RDO analysis (the majority of the placebo patients were treated with certolizumab from Week 16) of these one year data, the difference between the placebo and the certolizumab groups remained statistically significant (placebo vs. 200 mg, p≤0.01, placebo vs. 400 mg. p≤0.05). This gives a reassurance that the evidence of inhibition of structural damage for certolizumab have been obtained in a progressing study population.

Thus, considering the results of the conservative analysis at one year, and the high percentage of patients with no progression at two years, and also considering the ethical concerns about long-term placebo treatment for the collection of controlled X-ray data, a sustained effect of certolizumab pegol on structural damage is judged to be acceptably documented.

- Additional secondary outcomes

Major clinical response
Major clinical response could only be assessed in Study CDP870-027 as this was the only study with treatment duration of greater than 6 months. Major clinical response (i.e. continuous ACR70 response for 6 months) was achieved in 12.5% and 1.0% of the certolizumab 200 mg q2w and placebo treated subjects, respectively (p<0.001).

ACR components
ACR components significantly improved during certolizumab pegol treatment, as expected according to the results of ACR responses shown above.

DAS28 and EULAR response rates
In each of the Phase 3 studies, the reduction from Baseline in DAS28 (ESR) was significantly greater (p<0.001) in the certolizumab pegol treatment groups compared with the corresponding placebo groups at all weeks. The onset of DAS28 (ESR) reduction was rapid with significant differences between the active and control groups, as early as measured at Week 1, which were maintained through the end of the study.

In Studies CDP870-027 and CDP870-050, the percent of subjects with a good EULAR response (defined as a responder) at Weeks 24 and 52 was greater in both active groups as compared with their respective placebo groups.

Health Outcome Measures
Physical function was assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI), the Physical Component Summary (PCS) and the Physical Function (PF) domain of the SF-36. Health-related quality of life was assessed by the SF-36 (PCS and Mental Component Summary [MCS] and all domains).
In the four Phase 3 studies, the decrease from Baseline in HAQ-DI at Week 24 ranged from -0.31 to -0.58 in the certolizumab pegol treated groups and from -0.07 to -0.15 in the placebo groups, respectively. In each Phase 3 study, the mean improvement from Baseline in the HAQ-DI at Week 24 in all studies and at Week 52 in CDP870-027 was significantly greater (p<0.001) in all certolizumab pegol treatment groups as compared with their respective placebo groups. The proportion of subjects who achieved a minimal clinically important difference (defined as -0.22) ranged from 46% - 55% in the certolizumab pegol treatment groups and was significantly greater than placebo (6% - 23%) (p<0.001). In the four Phase 3 studies, the change from baseline in the SF-36 PCS at Week 24 ranged from 5.3 to 8.0 in the certolizumab pegol treated groups as compared with -0.2 to 2.9 in the placebo groups. Clinically meaningful increases ($\geq$ 2.5) in the PCS were significantly greater in the certolizumab pegol treatment groups as compared with placebo (p<0.001) in each of the Phase 3 studies.

Ancillary analyses

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

A number of subgroup analyses were undertaken in pooled data from studies 027 and 050. Pooling of these two studies are considered appropriate, since these studies were closely similar. For most subgroups there were no marked differences in ACR20 response at Week 24, and no interaction warrants specific recommendations in relation to use and labelling.

Antibody formation
The overall incidence of anti-CDP870 antibodies in the four Phase 3 studies was 7%. The incidence of antibody was lower in the studies with background MTX (027, 050 and 014) compared to the monotherapy study (011), which is in line what has been seen for other anti-TNF agents. The overall incidence of antibodies was consistently higher in the certolizumab 200 mg plus MTX dose group (8.5% to 10.7%) compared to the 400 mg plus MTX group (1.6% to 2.1%). However, there were no differences in ACR response rates among these two dose groups in studies 027 and 050. These data support a combination with MTX as the first treatment option, as the applicant has applied for. In studies 027 and 050 (pooled ACR20 data), presence of antibodies resulted in less responders,

particularly in the 200 mg q2w group (16% vs. 10% for 400 mg q2w). In the group positive for antibodies, 43.5% (200 mg q2w) and 50% (400 mg q2w) were responders, vs. 60% in the antibody negative groups. In samples with neutralizing anti-CDP870 antibodies, no cross-reactivity was seen with adalimumab, etanercept or infliximab. In addition, no cross-reactivity with certolizumab was shown in samples shown to be positive for infliximab antibodies.

- Clinical studies in special populations

The plasma concentrations, together with demographic information and antibody data, were used for performing population PK meta-analyses (refer to section on Pharmacokinetics above).

- Supportive studies

Study CDP870-014

Table 11   ACR response rates at Week 24 in study CDP870-014

	Placebo + MTX	**CDP870 400 mg + MTX**
N	118	122
ACR20		
Responder (%)	27 (22.9%)	56 (45.9%)
Odds ratio vs. PBO (95% CI)[a] P-value[b]		3.1 (1.7, 5.5) <0.001
ACR50		
Responder (%)	7 (5.9%)	22 (18.0%)
Odds ratio vs. PBO (95% CI) [a] P-value[b]		3.6 (1.5, 9.0) ≤0.01
ACR70		
Responder (%)	2 (1.7%)	0
Odds ratio vs. PBO (95% CI) [a] P-value[b]		NC / NS

In study 014, for the ACR20 response rate at Week 24 there was a statistically significantly result in favour of certolizumab pegol 400 mg + MTX vs. placebo + MTX. However, the response rate (46%) and observed difference (23%), was lower than observed with other anti-TNF agents in a similar population, and thus the clinical relevance of these results was questioned. Also for secondary endpoints, the data were not fully convincing. Due to these results, the applicant studied q2w dosing in the subsequent studies 027 and 050. If comparing the results from studies 027 and 050, the dose regimen 400 mg q4w appears inferior to 200 mg and 400 mg q2w dosing in terms of efficacy; however, no direct comparison of the q2w and q4w dosing regimen is available. The alternative posology of 400 mg q4w as originally proposed by the applicant was therefore not accepted for inclusion in the SPC.

Study CDP870-011

Table 12   ACR response rates at Week 24 in study CDP870-011

	Placebo (N=109)	**CDP870 400 mg (N=111)**
N	108	110
ACR20		
Responder (%)	10 (9.3%)	50 (45.5%)
Odds ratio vs. Placebo (95% CI) P-value		8.2 (3.8, 17.4) <0.001
ACR50		
Responder (%)	4 (3.7%)	25 (23%)
P-value		<0.001
ACR70		

Responder (%)	0	6 (5.5%)
P-value)		<0.013

In study 011, for ACR20 response a statistically significantly result was obtained with certolizumab pegol monotherapy vs. placebo in a population who previously had failed DMARD therapy. The observed difference was 36%. Similar results were seen for secondary endpoints. Overall, this result is clinically relevant, and may support effect on signs and symptoms of monotherapy in this population. However, due to a higher response rate where certolizumab pegol is added to MTX, and a higher degree of antibody development in subjects treated with monotherapy, combination with MTX has been proposed by the applicant as the first option. However, in patients who are intolerant to MTX, or when continued treatment with MTX is not appropriate, monotherapy can be accepted. This is reflected in the therapeutic indications in the SPC. Add-on to other DMARDs has not been studied; this information has been added to the SPC.

<u>Self-administration</u>
Self-administration was studied in the open label study CDP870-051, where some patients participated in a substudy. Self-administration was considered an acceptable option by the vast majority of those patients and is with adequate labeling statements, an acceptable option. The applicant has included instructions in the product information addressing self-administration, which are considered appropriate.

Clinical safety

The clinical safety data supporting this application derives from four adequate and well-controlled, double blind, international Phase 3 studies in adult patients with RA and their open-label extensions. Pooled data from Phase 2 studies and from Phase 1 studies in healthy subjects were also used.

- Patient exposure

There were a total of 2,367 subjects with RA who have received at least one dose of certolizumab pegol; 640 subjects received a dose of 200 mg q2w and 513 who received a dose of 400 mg q4w. Most subjects received medication for up to 24 months; 145 received certolizumab pegol for $\geq$ 48 months. These numbers are sufficient to meet ICH recommendations.

In the placebo-controlled studies, subjects in the 'All CDP870 Doses group' had a more than 4-fold longer duration of exposure than the placebo group (957 vs. 225 pt-yrs). The exposure in the population of open-label plus placebo-controlled subjects was 4065 pt-yrs, compared with 957 pt-yrs for the placebo-controlled studies. Given the large withdrawal of placebo subjects due to lack of efficacy after 16 weeks of treatment in studies 027 and 050, only 50 out of 647 placebo subjects were exposed beyond 6 months, which limits the safety data base.

- Adverse events

A common treatment-emergent adverse event (TEAE) was defined as any event occurring in ≥3% of subjects in any certolizumab pegol treatment group and at a rate greater than in the placebo group in at least 1 certolizumab pegol group. Table 13 is a summary of TEAEs by system organ class (SOC) and includes all SOCs, as well as high level terms (HLT) for which the incidence in any CZP treatment group was ≥3% or greater than in the placebo group.

There were a greater proportion of subjects experiencing both TEAEs and serious adverse events (SAE) in the certolizumab group compared with the placebo group. Additionally, the proportions of subjects experiencing both TEAEs and SAEs in open-label studies were greater than in placebo-controlled studies. The most common TEAEs and SAEs in certolizumab treated patients were infections and musculoskeletal disorders, as expected for the use of an anti-TNF drug in subjects with RA.

Table 13 *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 n (%)	PBO N=647 IR/ER[b]	CZP 200 mg q2 N=640 n (%)	CZP 200 mg q2 N=640 IR/ER[b]	CZP 400 mg q2w N=635 n (%)	CZP 400 mg q2w N=635 IR/ER[b]	CZP 400 mg q4w N=278 n (%)	CZP 400 mg q4w N=278 IR/ER[b]	All CZP Doses N=1774 n (%)	All CZP Doses N=1774 IR/ER[b]
Total Exposure in Patient-Years	224.9		396.0		410.2		106.7		957.4	
Any Adverse Event	404 (62.4%)	323.41 561.44	434 (67.8%)	239.58 452.70	426 (67.1%)	222.24 441.23	216 (77.7%)	447.19 705.41	1260 (71.0%)	286.45 535.27
Blood and lymphatic system disorders	24 (3.7%)	10.12 19.18	52 (8.1%)	13.41 20.19	45 (7.1%)	11.17 14.62	6 (2.2%)	5.26 6.95	111 (6.3%)	11.64 16.30
Cardiac disorders	13 (2.0%)	5.35 6.12	20 (3.1%)	4.95 7.30	22 (3.5%)	5.26 6.37	9 (3.2%)	7.93 11.29	61 (3.4%)	6.20 8.30
Ear and labyrinth disorders	5 (0.8%)	2.06 2.04	9 (1.4%)	2.21 2.43	9 (1.4%)	2.14 2.36	5 (1.8%)	4.38 4.34	26 (1.5%)	2.62 2.80
Endocrine disorders	1 (0.2%)	0.41 0.41	5 (0.8%)	1.22 1.22	4 (0.6%)	0.95 1.18	0	0	11 (0.6%)	1.10 1.20
Eye disorders	15 (2.3%)	6.23 8.98	20 (3.1%)	4.98 6.81	33 (5.2%)	8.08 9.43	7 (2.5%)	6.16 7.82	69 (3.9%)	7.10 8.90
Gastrointestinal disorders	88 (13.6%)	39.92 60.39	85 (13.3%)	22.87 38.68	82 (12.9%)	21.37 33.49	57 (20.5%)	56.09 80.79	277 (15.6%)	30.85 47.61
Gastrointestinal and abdominal pains (excl oral and throat)	11 (1.7%)	4.54 6.12	20 (3.1%)	4.97 6.32	16 (2.5%)	3.82 4.72	8 (2.9%)	7.09 9.56	51 (2.9%)	5.19 6.40
Diarrhoea (excl infective)	18 (2.8%)	7.49 8.98	10 (1.6%)	2.47 3.16	9 (1.4%)	2.14 2.36	16 (5.8%)	14.42 18.24	44 (2.5%)	4.47 5.50
General disorders and site administration conditions	110 (17.0%)	51.68 73.04	97 (15.2%)	26.88 41.11	78 (12.3%)	20.58 35.61	47 (16.9%)	45.83 68.63	272 (15.3%)	30.78 49.11
Injection and infusion site reactions	42 (6.5%)	18.07 33.05	42 (6.6%)	10.87 17.03	37 (5.8%)	9.27 17.45	17 (6.1%)	15.31 26.06	113 (6.4%)	11.99 21.30
Asthenic conditions	27 (4.2%)	11.45 13.06	26 (4.1%)	6.56 9.24	19 (3.0%)	4.59 4.95	18 (6.5%)	16.48 20.85	76 (4.3%)	7.86 9.70
Febrile disorders	11 (1.7%)	4.53 5.71	21 (3.3%)	5.19 7.05	18 (2.8%)	4.32 6.13	5 (1.8%)	4.37 4.34	49 (2.8%)	4.98 6.70
Pain and discomfort NEC	11 (1.7%)	4.54 5.30	7 (1.1%)	1.72 1.70	4 (0.6%)	0.95 0.94	9 (3.2%)	7.94 9.56	28 (1.6%)	2.83 3.10
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

Table 13 *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 n (%)	PBO N=647 IR/ER[b]	CZP 200 mg q2 N=640 n (%)	CZP 200 mg q2 N=640 IR/ER[b]	CZP 400 mg q2w N=635 n (%)	CZP 400 mg q2w N=635 IR/ER[b]	CZP 400 mg q4w N=278 n (%)	CZP 400 mg q4w N=278 IR/ER[b]	All CZP Doses N=1774 n (%)	All CZP Doses N=1774 IR/ER[b]
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
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, puerpium 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
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.

- Serious adverse event/deaths/other significant events

Serious adverse events (SAE)

The common SAE profile of certolizumab pegol is as expected for the use of an anti-TNF drug in patients with active RA. The most common SAEs were infections. In the placebo-controlled studies, the overall incidence rate of SAEs was greater in the active treatment group compared with placebo (10.7% vs. 6.6%). Furthermore, a greater percentage of patients in the certolizumab group of the All

Studies population experienced SAEs compared with that group of the placebo-controlled trials (26% vs 10.7%). In an effort to take into account duration of exposure between groups, both event rates and incidence rates were calculated. For event rates in the 'All CDP870 doses', there was also an increase in the CDP870 group (28.7% vs 23.7%). A comparison of incidence rates between All CDP870 doses reveals no increase with longer term exposure (17.0 in 'All Studies' compared with 20.7 per pt-yrs in placebo-controlled studies). The certolizumab pegol 400 mg every 4 weeks treatment group had a higher incidence rate of SAEs compared with the other active treatment groups. This is consistent with the data for TEAEs.

Deaths
A total of 33 deaths were reported, 10 of which occurred in placebo-controlled trials (9 of which were receiving certolizumab pegol) and 23 occurred in open-label studies. Fourteen certolizumab pegol treated patients experienced fatal cardiac events, three cardiopulmonary failure or cardiogenic shock, and two fatal vascular events, including cerebrovascular accident and pulmonary embolism. Seven subjects experienced fatal infection events, four fatal malignancies and three died due to trauma. The majority of deaths were from cardiac and infectious causes, a pattern similar to that observed in other biologically-treated RA subject populations. Six of the deaths previously labelled as 'non-related', could well be related to certolizumab treatment. This conclusion is agreed.

Infections
In the placebo-controlled studies, there was an increase in risk for infection in subjects receiving certolizumab pegol, compared with subjects receiving placebo. There was also an increase in risk for severe and serious infections, and a slight increase in risk for infection TEAEs leading to withdrawal, for subjects receiving certolizumab pegol as compared with those receiving placebo. The occurrence of the most frequent infections was similar in the placebo-controlled studies and the All Studies RA Population. There was no increase in incidence of infection with increased certolizumab pegol exposure.

In the placebo-controlled studies, the most frequently seen infections included upper respiratory tract infections, nasopharyngitis, urinary tract infections, and lower respiratory tract and lung infections. There were more events of urinary tract infections, bacterial infections, and viral infections in subjects receiving certolizumab pegol q2w, vs. certolizumab pegol q4w, with a difference of ≥3% in most cases.

Table 14   *Summary of the most commonly occurring serious infections from the placebo-controlled studies.*

High Level Term Preferred 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 (%)		
Exposure in Patient-Years	224.9	396.0	410.2	106.7	957.4
Any Event in the Infections and Infestations SOC	4 (0.6) 1.65/100py	24 (3.8) 5.95/100py	29 (4.6) 7.04/100py	5 (1.8) 4.38/100py	62 (3.5) 6.34/100py
Tuberculous infections[b]	0	5 (0.8)	4 (0.6)	0	9 (0.5)
Disseminated tuberculosis	0	3 (0.5)	1 (0.2)	0	4 (0.2)
Peritoneal tuberculosis	0	1 (0.2)	0	0	1 (0.1)
Pulmonary tuberculosis	0	1 (0.2)	0	0	1 (0.1)
Lymph node tuberculosis	0	0	1 (0.2)	0	1 (0.1)
Tuberculosis	0	0	2 (0.3)	0	2 (0.1)
Lower respiratory tract and lung infections	1 (0.2)	3 (0.5)	5 (0.8)	0	9 (0.5)
Pneumonia	0	3 (0.5)	4 (0.6)	0	8 (0.5)
Lower respiratory tract infection	1 (0.2)	0	0	0	0
Obstructive chronic bronchitis with acute exacerbation	0	0	1 (0.2)	0	1 (0.1)

Tuberculosis:

In the All Studies RA Population, 30 subjects experienced 32 events of tuberculosis. Fifteen had pulmonary tuberculosis, 5 had tuberculosis, 5 disseminated tuberculosis, 1 peritoneal tuberculosis, 3 subjects had lymph node tuberculosis, and 2 subjects had tuberculous pleurisy. In the long-term, open-label studies, only 2 subjects from low-incidence countries had tuberculosis compared with 27 subjects in high-incidence countries. All but one of the certolizumab pegol -treated subjects who developed tuberculosis infections were receiving concomitant MTX and 10 of 30 were receiving corticosteroids. Most cases (26 of 30) occurred after 12 weeks of therapy. Furthermore, 23 of these cases occurred with the 400 mg q2w dose, five with 200 mg q2w and two with 400 mg q4w.

Following the clinical database cut-off date of 31-Aug-2007, up to the safety database late cut-off date of 29-Feb-2008, four additional cases of tuberculosis were reported, at least three all from countries with a high prevalence of latent tuberculosis and all were taking concomitant MTX.

It can be concluded that, as expected for an anti-TNF agent, certolizumab pegol is associated with an increased risk of tuberculosis, frequently with disseminated or extrapulmonary clinical presentation. The tuberculosis incidence rate observed with certolizumab pegol appears high, but it is noted that subjects enrolled in these studies were from countries with high tuberculosis incidence rates and often had a positive PPD tests at baseline. The applicant has also provided a summary on available experience with use of prophylactic anti-TB treatment in patients with suspected latent TB treated with certolizumab pegol. Although these data are limited, they provide some reassurance regarding use of certolizumab pegol in subjects who are treated for suspected latent TB, and support the proposed recommendations in the SPC.

Other infections

The current data also confirm that certolizumab pegol is associated with an increase in opportunistic infections, as well as with reactivation of viral infections, which has been described for the other anti-TNF agents.

There is one hepatitis B case (no prior history of hepatitis). Several cases of herpes infections were identified (84 in 63 subjects [3.6%, 6.5/100 pt-yrs]]for CDP870 and 9 cases in 8 subjects [1.2%, 3.3/100 pt-yrs] for placebo. In the All Studies RA Population, there were five opportunistic fungal infections: 1 fungal oesophagitis, 2 oesophageal candidiasis, 1 geotrichosis, and 1 Pneumocystis; where two (geotrichosis and Pneumocystis) were serious. Two subjects treated with CDP870 and MTX developed Legionella pneumonia. One additional subject experienced an infection of nocardiosis. Through the safety database late cut-off date of 29-Feb-2008, 1 new case of histoplasmosis was reported.

Malignancies

In the placebo-controlled studies, there were a total of 10 malignancies identified (excluding non melanoma skin cancers), including 9 subjects receiving certolizumab pegol and one on placebo. Those included tongue neoplasm, lung cancer, B cell lymphoma, oesophageal carcinoma, hepatic neoplasm, uterine cancer, metastases to CNS, colon cancer, testicular cancer and bladder cancer (placebo). Additionally, 3 subjects had basocellular carcinoma of the skin (all serious). Four of these had brief exposure to certolizumab pegol (less than 50 days) and two had received only a single dose.

In the All Studies population, there were 24 cases of malignancies (23 subjects), all on certolizumab pegol (2 lymphomas, 4 gastrointestinal, 2 breast, 6 genitourinary, 5 respiratory tract, 1 each of endocrine, renal, skin and occult malignancies, 9 with basocellular carcinoma of the skin). One additional case was identified through cut-off date of 29-Feb-2008 (gastric cancer).

Autoimmune disorders

In the placebo-controlled studies, 145 of 868 subjects (16.7%) in the All CDP870 Doses group and 43 of 357 subjects (12.0%) in the placebo group experienced a shift from negative to positive antinuclear antibody (ANA) titer at any time during the study. A shift to elevated anti-dsDNA titers occurred in 30 of 1369 subjects (2.2%) in the All CDP870 Doses group and 5 of 479 subjects (1.0%) in the placebo group. In the placebo controlled population, one subject on certolizumab pegol experienced an SAE of

lupus-like syndrome, and in the All Studies population, a total of 6 subjects experienced lupus-like events. These events are consistent with previous reports of events observed with other TNF-blocking agents, and are addressed in the SPC.

Cardiovascular disorders
There was an increase in the percentage of subjects with hypertensive events in the certolizumab pegol group vs. placebo (5.1 vs. 1.2%, respectively). However, there was no difference between the certolizumab pegol treatment groups and placebo in the mean change from baseline in systolic or diastolic blood pressure, nor the shifts of ≥ 5 mmHg in diastolic blood pressure. In the placebo-controlled studies, 16 subjects (0.9%) in the All CDP870 Doses group experienced SAEs of Cardiac disorders, vs. 3 subjects (0.5%) on placebo.

Congestive heart failure was reported in 10 patients. Use of anti-TNF agents is contraindicated in subjects with moderate to severe heart failure. Certolizumab pegol use should also be contraindicated and relevant warnings should be included, in accordance with wording for other agents of this class.

During the review process, the applicant submitted an additional in-depth analysis of a number of cardiovascular events. These data do not raise additional concern and support information included in the SPC. Furthermore, CV events are also addressed in the RMP.

Neurological events
The incidence of neurological adverse events was similar in certolizumab pegol -treated subjects and those receiving placebo. No cases of multiple sclerosis, optic neuritis, or other demyelinating diseases occurred in the RA Population studies. However, demyelination is a known class effect for anti-TNF agents and a warning has been added to the SPC (4.3).

Haematological disorders
In the placebo-controlled studies, a greater percentage of subjects receiving certolizumab pegol at any dose, compared with placebo, experienced haematological adverse events (9.0% vs. 5.4%). The most common haematological disorders for certolizumab pegol and placebo were eosinophilia (1.7%, 3.05/100 pt-yrs, and 0.5%, 1.23/100 pt-yrs, respectively), aPTT prolonged (1.4%, 2.42/100 pt-yrs and 0.3%, 0.82/100 pt-yrs, respectively), and anaemia (1.4%, 2.42/100 pt-yrs and 1.2%, 3.29/100 pt-yrs, respectively)

Bleeding events
In the placebo-controlled studies, SAEs related to bleeding occurred in 6 subjects on certolizumab pegol and one on placebo. In CDP870-treated subjects, serious bleeding events included haematoma, melaena (due to epistaxis), 2 cases of menorrhagia, metrorrhagia and bleeding nasal polyp.

In the open-label studies, an additional 6 certolizumab pegol -treated subject experienced serious bleeding events. These included haematuria, 4 metrorrhagia and post-procedural haemorrhage. Through the late cut-off date of 29-Feb-2008, seven additional cases were reported: haematuria, gastrointestinal haemorrhage, and uterine haemorrhage, rectal haemorrhage, uterine haemorrhage, purpura, and melaena.

Although the data did not suggest an increased incidence in "any bleeding event", there is the suggestion that treated subjects are at greater risk for "dysfunctional uterine bleeding". The frequency for the placebo group was 0.5% (incidence rate of 1.23), compared with 0.9% (incidence rate of 1.61) for certolizumab pegol. Also, 3/6 (50%) SAEs in placebo-controlled studies and 4/6 (67%) in the "all studies" population were due to this cause.

Available data do not reveal an association between specific coagulation abnormalities and general bleeding events. Based on a review of all cases of "dysfunctional uterine bleeding" occurring in all studies, it can be concluded that in the RA programme there was a slightly higher incidence of "dysfunctional uterine bleeding" during the placebo-controlled phase, and there were 3 SAE; all in the certolizumab group. 'Uterine bleeding disorders' is added in section 4.8 of the SPC. In the RMP, serious bleeding is included as a potential risk, which is considered sufficient.

Hepatic events
There was a low incidence of hepatobiliary events during the placebo-controlled studies. The incidence rate did not increase during open-label treatment. The most common hepatic events were effects in liver function analyses and included increased alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase (2.29, 1.65, and 1.35/100 pt-yrs, respectively). The incidence rate of these events in the placebo-controlled studies was 4.79, 3.45, and 2.32/100 pt-yrs, respectively, in the All CDP870 Doses group. Serious adverse events were more common in the certolizumab pegol treatment group, however most were either cholelithiasis or cholecystitis. There was one case of autoimmune hepatitis. Overall, the hepatic events described in the study population do not constitute any alarming signal.

Local injection reactions
The proportion of subjects experiencing either a skin and/or subcutaneous disorder, including local injection site reactions, was low. Interestingly, subjects who had developed antibodies to certolizumab pegol had a lower incidence of injection site reactions. There is no indication of severe/serious reactions linked to either the drug itself or to the development of antibodies against it.

Hypersensitivity reactions
There was one clear case of serious hypersensitivity and one case of serum sickness. These data do not raise concern: however, hypersensitivity is a common complication with anti-TNF agents and an appropriate warning has been added to the SPC.

Respiratory disorders
The incidence of non-infectious respiratory events was not markedly increased in certolizumab pegol treated subjects compared with placebo, and there was no evidence of an increase in these events over prolonged periods of exposure. There were three certolizumab pegol-treated subjects in placebo-controlled studies who experienced lung infiltration. While associations to MTX cannot be excluded, cases of interstitial lung diseases/pneumonitis have been reported with other drugs of this class, and this is reflected in the SPC.

- Laboratory findings

In general, changes in haematology parameters appear to be consistent with those expected from lower disease activity. From preclinical data there were reports of prolongation of aPTT which has been discussed in this application as an *in vitro* phenomenon with several of the commercially available assay kits. Further, it can be concluded that certolizumab pegol does not appear to have a clinically meaningful deleterious effect upon liver function tests, renal function tests, albumin and total protein, glucose, total calcium or electrolytes.

- Safety in special populations

In placebo controlled studies, the overall incidence of TEAEs and SAEs appeared with higher frequencies in the ≥ 65 years age group (compared to the 18 to 64 years age group). This is not unexpected, since certain events would be expected to be more common in a more elderly group, and a higher sensitivity in elderly for, e.g. infections is not unlikely. However, the number of subjects in this age group was small, making it difficult to draw meaningful conclusions. The applicant will collect additional data in the planned registries. Further, a warning statement has been added to the SPC.

The current experience with certolizumab pegol treatment during pregnancy is far too limited to draw any conclusions. The lack of adequate data on use of certolizumab pegol during pregnancy is stated in the SPC. Plans for pregnancy follow-up in the post marketing setting is part of the follow-up measures in the area of pharmacovigilance.

- Safety related to drug-drug interactions and other interactions

When looking at the overall infection data, there was no clinically meaningful difference in the proportion of patients experiencing an infection between those receiving MTX and those who did not.

- Discontinuation due to adverse events

The adverse events most often leading to withdrawal in both the placebo-controlled and the All Studies population were Infections and Infestations. In both populations, tuberculous infections were the most commonly occuring infection leading to withdrawal. The proportion of patients withdrawing because of an infection increased from 1.8% to 4.6% over time. The discontinuation pattern for certolizumab pegol treated patients does not raise concerns related to either efficacy or safety, and is not considered to have had a negative impact on the interpretation of the study results.

- Post marketing experience

No post-marketing experience with certolizumab pegol has been available at the time of Marketing Authorization.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Pharmacovigilance activities (routine and additional)	Risk minimization activities (routine and additional)
Important identified risks		
Infections, including serious opportunistic infections	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of infections, including serious opportunistic infections, and their characteristics in PSURs.	• SmPC Section 4.8: addresses the risk of infections and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.4: includes a warning statement to perform screening tests for TB prior to initiating therapy, as well as appropriate anti TB treatment in cases of latent TB infection. • SmPC Section 4.3: includes active TB and other severe infections as Contraindications • Educational program
Important potential risks		
Malignancies, including lymphoma	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluate the risk of malignancies, including lymphoma, and its characteristics in PSURs	• SmPC Section 4.8: addresses the risk of malignancies, including lymphoma, and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • Educational program

Safety concern	Pharmacovigilance activities (routine and additional)	Risk minimization activities (routine and additional)
Congestive heart failure and ischemic cardiac events	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of CHF and ischemic cardiac events and their characteristics in PSURs	• SmPC Section 4.8: addresses the risks of CHF and cardiac ischemic events and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.3: includes moderate to severe heart failure under Contraindications • Educational program
Demyelinating-like disorders	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of demyelinating-like disorders and its characteristics in PSURs	• SmPC Section 4.4: includes Special warnings and precautions for use • Educational program
Aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, leukopenia	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risks of pancytopenia, aplastic anemia, thrombocytopenia, neutropenia, and leukopenia and their characteristics in PSURs	• SmPC Section 4.8: addresses the risks of aplastic anemia, neutropenia, thrombocytopenia, leukopenia, and pancytopenia, and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • Educational program
Serious bleeding events	• Routine pharmacovigilance activities • Evaluation of the risk of bleeding disorders and its characteristics in the PSURs	• SmPC Section 4.4: includes Special warnings and precautions for use, and describes the aPTT assay interaction and explains the use of caution in the interpretation of abnormal coagulation test results. • Educational program
Lupus and lupus-like illness	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of autoimmune disorders and its characteristics in PSURs	• SmPC Section 4.8: addresses the risk of autoimmune disorders and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • Educational program
Immunogenicity	• Routine pharmacovigilance activities • Evaluation of the risk of immunogenicity and its characteristics in PSURs	• SmPC Section 5.1: addresses the risk of immunogenicity and its characteristics
Hepatitis B reactivation	• Routine pharmacovigilance activities • Evaluation of the risk of hepatitis B reactivation and its characteristics in PSURs	• SmPC Section 4.8: addresses the risk of hepatitis B reactivation and its characteristics in the SmPC • SmPC Section 4.4: includes Special warnings and precautions for use to perform screening tests for HBV prior to initiating therapy • Educational program
Important missing information		
Pregnancy and lactation	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk on pregnancy outcomes gathered in PSURs	• SmPC Section 4.6: addresses the risk of use during pregnancy and lactation • SmPC Section 4.8: addresses pregnancy outcome risk (spontaneous abortion)

Safety concern	Pharmacovigilance activities (routine and additional)	Risk minimization activities (routine and additional)
Children and adolescents	• Routine pharmacovigilance activities • Active surveillance of off-label use of CZP in children under 18 in registries • Evaluation of the risk information gathered in PSURs • Planned juvenile idiopathic arthritis study (RA0016)	• SmPC Section 4.2: includes information on risk of use in children and adolescents
Elderly	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk information gathered in PSURs	• SmPC Section 4.2: includes information on the risk of use in elderly patients
Patients with renal or hepatic impairment	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk for these patients and any special characteristics in PSURs	• SmPC Section 5.2: includes PK properties • SmPC Section 4.2: describes the absence of data on Patients with renal or hepatic impairment • The absence of data on patients with renal or hepatic impairment is described in the US PI.
Immune function / vaccination	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk information gathered in PSURs • Risk assessment in vaccine study (RA0017)	• SmPC Section 4.4: includes Special warnings and precautions for use
Potential for overdose	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of overdose and its characteristics in PSURs	• SmPC Section 4.9: includes a description on the risk of overdose • An educational program will serve to minimize the risks of erroneous administration.
Potential for medication errors	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of medication errors and its characteristics in PSURs	• SmPC Section 4.2: includes posology • An educational program will serve to minimize the risks of erroneous administration by clearly describing the method of administration and the amount to be administed.
Off-label use	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluation of the risk of off-label use and its characteristics in PSURs	• SmPC Section 4.1: includes therapeutic indications • An educational program will serve to minimize the risks of off-label use.
Concomitant use with DMARDs other than MTX	• Routine pharmacovigilance activities • Active surveillance through registry activities • Risk assessment in Study C87094 • Evaluation of the risk information gathered in PSURs	• SmPC Section 4.5: includes information on risk of use with DMARDs other than MTX
Previous use of anti-TNF therapy	• Routine pharmacovigilance activities • Active surveillance through registry activities • Evaluate in Study C87094 • Address previous anti-TNF use in PSURs	• SmPC Section 4.4: includes information on risk of use with previous hypersensitivity to another anti-TNF therapy

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The documentation provided with the application demonstrates consistent batch-to-batch production of Cimzia achieving a consistent quality for the drug substance and the drug product. The fermentation, purification and pegylation of the drug substance, Certolizumab pegol (CDP870), are adequately controlled and validated. The drug substance has been extensively characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. In addition, the viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. In general, appropriate drug substance and drug product specifications have been set.

Non-clinical pharmacology and toxicology

An adequate non-clinical programme has been conducted for certolizumab pegol. The preclinical observations did not raise major concerns against the use of certolizumab pegol in humans at the proposed clinical use.

Fertility data in rats using the homologous agent cTN3 PF showed that sperm motility parameters tended to be lower in the treated groups and the motility was significantly decreased in the high-dose group (100 mg/kg). While the relevance of these findings for humans is unknown, an effect of anti-TNFα therapies on sperm morphology and motility in humans cannot be ruled out. A clinical evaluation of the effect of certolizumab pegol treatment on male sperm quality was requested as a follow-up measure.

Efficacy

Four multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical studies in patients with active RA were submitted, and one additional Phase 2 study with subcutaneous administration. In two of the Phase 3, placebo was compared with 400 mg certolizumab pegol every 4 weeks (q4w), in one study as monotherapy (011) and in one as add-on to MTX. In the other two Phase 3 studies (027 und 050), placebo was compared with 200 mg (started by 3 loading doses of 400 mg) or 400 mg certolizumab pegol every 2 weeks (q2w) as add-on therapy to MTX. The latter two Phase 3 studies were considered pivotal as they evaluated the dosing regimen applied for.
In the Phase 3 studies 011, 014 and 027, a lyophilized formulation was used, while a liquid formulation, the proposed commercial form, was used in study 050. All clinical studies were performed according to GCP principles.

The primary endpoint of ACR20 at Week 24 was met in all studies and the differences to the placebo control are statistically significant and clinically relevant. In study 027, structural joint damage was assessed radiographically and expressed as change in mTSS at Week 52, compared to baseline. Cimzia patients demonstrated significantly less radiographic progression than patients receiving placebo. In the placebo group, 52% of patients experienced no radiographic progression at Week 52 compared to 69% in the Cimzia 200 mg treatment group. Sustained inhibition of progression of structural damage was demonstrated in a subset of 449 of these patients who completed at least 2 years of treatment with Cimzia and had evaluable data at the 2-year timepoint.

The pivotal Phase 3 studies with certolizumab pegol demonstrated significant clinical efficacy in all secondary endpoints such as ACR50, ACR70 responses, DAS28 (ESR), Improvement in Physical Function and Health-related Quality of Life measures.

In the monotherapy study (011) using certolizumab pegol 400 mg q4w, the ACR20, ACR50, and ACR70 responses were clinically and significantly better than placebo, although the magnitude of the response was not as robust as in the combined therapy studies 027 and 050.

In the studies 027 and 050, certolizumab pegol 200 mg q2w or 400 mg q2w showed clinically and statistically significant better results compared to placebo in all important efficacy measures. There were no clinically relevant differences between the 200 mg q2w and 400 mg q2w groups (with background MTX); therefore the lower effective dose is recommended.

There were slight numerical differences in PK and efficacy between the optimized liquid and lyophilized formulations, but these differences are not considered of clinical relevance.

Safety

In summary, there were a total of 2,367 subjects with RA who have received at least one dose of certolizumab pegol, 640 of which received a dose of 200 mg q 2wk and 513 who received a dose of 400mg q 4w. Most subjects received medication for up to 24 months; 145 received CZP for $\geq$ 48 months. These numbers are sufficient to meet ICH recommendations.

There were a greater proportion of subjects experiencing both TEAEs and SAEs in the certolizumab pegol group compared with the placebo group. Additionally, the proportions of subjects experiencing both TEAEs and SAEs in open-label studies were greater than that in placebo-controlled studies. The most common TEAEs and SAEs in certolizumab pegol treated patients were infections as expected for the use of an anti-TNF drug in subjects with RA and general or injection site disorders.

Of the total of 33 deaths in RA studies, 10 occurred in placebo-controlled trials (9 of which were receiving certolizumab pegol) and 23 occurred in open-label studies. The majority of deaths were from cardiac and infectious causes.

From the available data it can be concluded that certolizumab pegol is associated with an increased risk of tuberculosis (TB), frequently with disseminated or extrapulmonary clinical presentation. The applicant has also provided a summary on available experience with use of prophylactic anti-TB treatment in patients with suspected latent TB treated with certolizumab pegol. Although these data are limited, they provide some reassurance regarding use of certolizumab pegol in subjects who are treated for suspected latent TB, and support the recommendations in the SPC. The current data also confirm that certolizumab pegol is associated with an increase in opportunistic infections, as well as with reactivation of viral infections, which has been described for the other anti-TNF agents.

In the placebo-controlled studies, 9 of 10 subjects with malignancies were exposed to certolizumab pegol. In the open label studies, there were an additional 24 cases of malignancy. The uncertainties related to long-term use of TNF-alpha inhibitors and the potential risk for malignancy are well known concerns associated with use of anti-TNF agents. The potential risk for malignancy has to be weighed against the potential benefit of certolizumab pegol therapy in the indications applied for. This risk, together with appropriate precautions to take, are addressed in the product information, as well as in the RMP. Furthermore, long-term follow up of subjects in the studies undertaken as well as participation in ongoing patient registries in the rheumatoid arthritis population are subject of follow up measures (FUM).

Both congestive heart failure and hypertension have been documented to be associated with the use of agents of this class. Congestive heart failure occurred in 10 subjects. Hypertension was observed more frequently in subjects receiving certolizumab pegol compared with placebo, although there was no documented difference in the mean change from baseline blood pressure between the two groups.

The use of certolizumab pegol may be associated with an increased risk of "dysfunctional uterine bleeding". While the data do not reveal an increased incidence in "any bleeding event" associated with the use of certolizumab pegol, there is the suggestion that treated subjects are a greater risk for "dysfunctional uterine bleeding". This type of bleeding event has been reported in clinical trials using

certolizumab pegol in other indications; however, it has not been reported with other agents of this class.

There were small numbers of subjects who developed auto-antibodies and who developed a lupus-like illness or rash. Additionally, 3 subjects experienced lung infiltration, suggestive of interstitial lung disease/pneumonitis. There were no cases of demyelinating disorders.

There were no clinically meaningful differences in tolerability between the liquid (formulation for marketing) and lyophilized formulations were observed. Furthermore, no clinically meaningful difference in safety between the two doses, 200 mg and 400 mg every 2 weeks, and no clinically relevant effects of certolizumab pegol on clinical laboratory parameters, vital signs, physical examinations, or body weight were observed

Overall, the profile of certolizumab pegol is similar to that of other TNF-alpha blockers and the SPC is in line with those of other anti-TNF agents with respect to sections 4.4 and 4.8. Furthermore, the RMP addresses the safety concerns noted above.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation has been performed with acceptable methodology.

Risk-benefit assessment

Benefits:
Studies 027 and 050 are pivotal since in those the posology applied for, 200 q2w, was studied. For the primary endpoint, ACR20 at Week 24, a statistically significant and clinically relevant effect on signs and symptoms was shown for certolizumab pegol in combination with MTX (in study 027: 14% placebo vs. 59%; study 050: 9% placebo vs. 57%). Also secondary endpoints addressing signs and symptoms, physical function and other, e.g. quality of life related measures, showed statistically significant and clinically relevant better efficacy with certolizumab pegol as add-on to MTX compared with placebo + MTX. The sensitivity analyses have not dealt with the withdrawals due to lack of response in a conservative way but any potential bias would probably be minor relative to the compelling statistical significance and magnitude of the effect. The results compare well with what has been demonstrated for other anti-TNF compounds. However, a shortcoming with the dossier is the lack of directly comparative data with other anti-TNF agents, since certolizumab pegol is at least the fourth anti-TNFα agent to be approved for marketing.

In study 027, 52 week data on signs and symptoms as well as joint damage were also obtained. The response rate dropped slightly (5-6%) for ACR20 at Week 52 vs. Week 24, while there was no difference for ACR50 and ACR70. These data support maintained effect on signs and symptoms during the 52 week period, and additional open-label extension data support a similar picture up to 2 years treatment.

Studies 011 and 014 used a q4w dosing. In study 011, a statistically significant result for ACR20 was obtained with certolizumab pegol monotherapy (45.5%) vs. placebo (9.3%) in a population who previously had failed DMARD therapy. Overall, this result is clinically relevant and may support effect on signs and symptoms of monotherapy in this population. However, due to a higher response rate where certolizumab pegol is added to MTX and a higher degree of antibody development in subjects treated with monotherapy, combination with MTX has been proposed by the applicant as the first option, while monotherapy may be considered for subjects who cannot be treated with MTX. This is agreed and reflected in the SPC.

In study 014, the ACR20 results at Week 24 were statistically significant in favour of certolizumab pegol 400 mg + MTX vs. placebo + MTX in a population who previously had failed DMARD therapy. However, the response rate (46%) and observed difference (23%) was lower than observed with other anti-TNF agents in a similar population, and thus the clinical relevance of these results was questioned. Also, for secondary endpoints the data were not fully convincing.

Comparing the results from study 014 with those from studies 027 and 050, the dose regimen 400 mg q4w appears inferior to 200 mg q2w dosing in terms of efficacy. In addition, data from 027 and 050 do not show any obvious increase in efficacy with 400 mg q2w compared with the 200 mg q2w dose regimen. The applicant proposes a loading dose of 400 mg at weeks 0, 2 and 4, which was used in the pivotal studies 027 and 050, followed by 200 mg q2w. Taken together, the proposed dose regimen is acceptable, although one could conclude that the dose selection is to some extent empirical. However, the option to use 400 mg q4w, which had been proposed as well, was not accepted for inclusion in section 4.2 of the SPC.

Statistically significant results have been demonstrated on structural joint damage up to 52 weeks. The findings have been found robust in appropriate sensitivity analyses. The results are consistent with a complete inhibition of structural damage. Additional x-ray data obtained following two years of treatment continue to support a sustained effect of certolizumab pegol on structural damage and thus, the proposed wording in the indication is accepted.

Long-term benefits are still uncertain, due to limited amount of data.

Risks:
Demonstrated risks
The safety profile of certolizumab pegol appears to be in line with the well known safety profile of anti-TNF agents, although long-term safety data are currently rather limited. Infections including serious and opportunistic cases were the most common adverse event/serious adverse event. The tuberculosis incidence rate observed with certolizumab pegol appears high (about 33 cases in the overall RA population), but it should be considered that subjects enrolled in these studies were from countries with high tuberculosis incidence rates and often had positive PPD tests at baseline.

Potential risks
The uncertainties related to long-term use of TNF-alpha inhibitors and the potential risk for malignancy are well known concerns associated with the use of TNF-alpha inhibitors. In the placebo-controlled parts of the studies, 9 of the 10 subjects with malignancies were exposed to certolizumab pegol, indicating an increased risk with the use of these agents even with shorter term exposure (up to 52 weeks). However, the observational time period (52 weeks) is too short to draw any definite conclusions. Long-term follow up of patients, monitoring via registries, education programme, as well as adequate labelling are of importance.

Although not a strong signal, there was a slightly higher incidence of 'dysfunctional uterine bleeding' in the RA programme; which is addressed in the SPC and the RMP.

Balance:
Certolizumab pegol, in combination with MTX, has in studies of up to 52 weeks duration in a RA population who previously had failed DMARD therapy, shown statistically significant, compelling and clinically relevant results on signs and symptoms of disease. The magnitude of the effect and overall results compare well with what has been demonstrated for other anti-TNF compounds.

X-ray data on structural damage are statistically significant and clinically promising over 52 weeks of treatment. Additional x-ray data obtained following two years of treatment continue to support a sustained effect of certolizumab pegol on structural damage, and thus, the proposed wording in the indication is accepted.

The safety profile is overall as expected for an anti-TNF agent, although long-term data are sparse. Infections and risk for malignancy are the main concerns in general. Adequate information in the SPC and follow-up measures are necessary to support a positive benefit/risk balance. The applicant has provided further details on the planned registry follow up; which is acceptable.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- the following additional risk minimisation activities were required: were required: see as detailed in the Annex "Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product to be implemented by the Member States".

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Cimzia in the following indication:

Cimzia, in combination with methotrexate, is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs 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."

was favourable and therefore recommended the granting of the marketing authorisation.