European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 March 2008
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REFUSAL ASSESSMENT REPORT
FOR
CIMZIA

International Nonproprietary Name:
certolizumab pegol

Procedure No. EMEA/H/C/740

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

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PRODUCT INFORMATION

Name of the medicinal product:	CIMZIA
Applicant:	UCB S.A. Allée de la Recherche 60 B-1070 Bruxelles Belgium
Active substance:	certolizumab pegol
International Nonproprietary Name/Common Name:	certolizumab pegol
Pharmaco-therapeutic group (ATC Code):	Selective immunosuppressive agents (L04AB05)
Therapeutic indication(s):	CIMZIA is indicated for treatment of severe, active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant or who are intolerant to or have medical contraindications for such therapies
Pharmaceutical form:	Powder and solvent for solution for injection
Strength:	200 mg
Route of administration:	Subcutaneous use
Packaging:	powder: vial (glass); Solvent: vial (glass)
Package sizes:	2 vials + 2 vials + 2 plastic syringes + 6 needles + 8 alcohol swabs

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant UCB S.A. submitted on 28 April 2006 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 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 Crohn's disease.

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the following countries: USA on 1 March 2006.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Steffen Thirstrup Co-Rapporteur: Tomas P Salmonson

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 28 April 2006.
- The procedure started on 24 May 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2006 (Annex 3.1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2006 (Annex 3.2).
- During the meeting on 18-21 September 2006, 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 21 September 2006 (Annex 3.3).
- The CHMP agreed to the request from the applicant dated 18 October 2006 for an additional 3-month extension of timeframe to submit responses to the List of Questions.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 April 2007. On 10 May 2007 the applicant submitted an update correcting an error in the clinical documentation.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 June 2007 (Annex 3.4).
- During the CHMP meeting on 18-21 June 2007, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and by the applicant (Annex 3.5).
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 August 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 25 September 2007 (Annex 3.6).
- During the BWP meeting on 8-10 October 2007 outstanding quality issues were addressed by the applicant in an oral hearing before the BWP
- During the CHMP meeting 15-18 October 2007, outstanding issues were addressed by the applicant during an oral explanation before the CHMP
- During the meeting on 12-15 November 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to CIMZIA on 15 November 2007.

1.3 Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Dr. P. Demolis Co-Rapporteur: Dr. S. Ormarsdottir

- The applicant submitted written notice to the EMEA on 5 December 2007 to request a re-examination of the CIMZIA CHMP opinion of 15 November 2007.
- During its meeting on 10-13 December 2007, the CHMP appointed Dr. P. Demolis as Rapporteur and Dr S. Ormarsdottir as Co-Rapporteur.
- The detailed grounds for the re-examination request were submitted by the applicant on 18 January 2008 (Appendix 2 of Final Opinion). The re-examination procedure started on 19 January 2008.
- The Rapporteur's Assessment Report was circulated on 22 February 2008 (Annex 3.7). The Co-Rapporteur's Assessment Report was circulated on 19 February 2008 (Annex 3.8).
- The CHMP adopted a List of Participants for an Ad-hoc Expert meeting to be held on 4 March 2008 together with the List of Question to be addressed by the experts, through written procedure 28 February 2008.
- During a meeting of the CHMP Ad-hoc Expert meeting on 4 March 2008, experts were convened to consider the grounds for re-examination. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP (Annex 3.9).
- The Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 13 March 2008 (Annex 3.10).
- During the CHMP meeting on 17-19 March 2008, the applicant presented an oral explanation before the CHMP on 18 March 2007.
- During the meeting on 17-19 March 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final Opinion recommending the refusal of granting a Marketing Authorisation for CIMZIA.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

CIMZIA has been developed for the treatment of active Crohn's disease, a chronic inflammation of the digestive tract, especially of the lower small intestine (ileum) and colon.

Certolizumab pegol, the drug substance of CIMZIA is a recombinant, humanized Fab' antibody fragment covalently bound to a maleimido terminated bis methoxypoly (ethylene glycol) modified lysine, PEG2MAL40K, through a thioether linkage. The Fab' antibody fragment is linked to ethylene glycol in order to extend its plasma half-life to that of the whole antibody.

Certolizumab pegol is directed against TNF-α and neutralizes soluble and membrane TNF-α, inhibits the binding of TNF-α to human p55 and p75 TNF receptors and inhibits LPS-induced cytokine production in human monocytes. Certolizumab pegol does not cause antibody or complement dependent cytotoxicity, and does not induce neutrophil degranulation or apoptosis in human peripheral blood-derived T-lymphocytes and monocytes.

The *originally claimed indication* was "for inducing clinical response and maintaining clinical response and remission in patients with active Crohn's disease who are intolerant, have medical contraindications or had insufficient response to prior therapy with corticosteroids with or without immunosuppressants and / or 5-amino salicylic acid (ASA) and analogues.

In addition, CIMZIA was indicated for inducing clinical response and maintaining clinical response and remission in patients with active Crohn's disease who have previously received infliximab."

After review of the dossier, the applicant proposed a revised indication as follows:

"CIMZIA is indicated for treatment of severe, active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant or who are intolerant to or have medical contraindications for such therapies."

The recommended dose is 400 mg dose divided into two sc injections at Weeks 0, 2 and 4 followed by 400 mg at 4 weekly intervals.

Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

2.2 Quality aspects

Introduction

Certolizumab pegol (CDP870), the drug substance of Cimzia is a recombinant, humanized Fab' antibody fragment covalently bound to a maleimido terminated bis methoxypoly (ethylene glycol) modified lysine, PEG2MAL40K, through a thioether linkage. The linkage of the Fab' antibody fragment to ethylene glycol is in order to extend its plasma half-life to that of the whole antibody. The variable region sequences of CDP870 Fab' were derived from a murine IgG2a antibody by CDR grafting with kappa light chain and gamma 1 heavy chain constant regions. The Fab' fragment is directed against TNF (alpha) and neutralizes the biological activity of TNF α. The CDP870 Fab' fragment is produced in *Escherichia coli*. Following purification by standard chromatographic methods, the CDP870 Fab' fragment is conjugated to PEG2MAL40K, through a cysteine that is located three amino acids from the carboxy terminus of the heavy chain fragment. A single molecule of PEG2MAL40K is covalently bound to each Fab' molecule. The resulting Fab'- PEG2MAL40K

conjugate is further purified and formulated in lactate 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 lyophilized formulation containing 200 mg/vial. Each vial is intended for single use, following reconstitution with sterile Water for Injection.

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 has been validated; however, the results for the three validation batches are not provided. This is considered acceptable as the results of the extensive amount of production batches satisfactorily demonstrate that the manufacturing process is in control and capable of producing a consistent and uniform product.

Control of materials has been adequately described and specifications for all starting materials, solvents etc. are provided. The reference standard for the identity assay, has been adequately characterised.

Impurities are satisfactorily described with respect to origin of the impurity, fate of the impurity and analytical control.

Stability results have been presented to support the proposed storage condition of 15 months at -20˚C.

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' through the C-terminal cysteine at position 227 of the heavy chain.

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'.

- Manufacture

Manufacturers

Genetic development
The generation and control of the expression plasmid, pTTOCDP870 is described in sufficient detail. CDP870 is a humanized Fab' version of the murine HTNF40 antibody, which binds to humanTNF alpha and is a potent neutralizer of TNF activity. The expression plasmid contains DNA encoding a complete light chain plus a truncated heavy chain consisting of VH, CH1 and a modified hinge region. The sequence of the γ1 hinge was changed from Cys-Pro-Pro-Cys to Cys-Ala-Ala to generate a hinge region with a single cysteine residue available for site-specific attachment of the PEG moiety. Detailed flow charts of the construction of the expression plasmid are provided. Expression is under control of the tac promoter. Both light and heavy antibody chains are fused to an OmpA leader sequence,

allowing translocation of the antibody chains to the E. coli periplasm. No DNA from the HTNF40 hybridoma is present in the genes encoding CDP870 Fab′.

Cell Banking
Cell banks of an *E.coli* strain (W3110) were manufactured using animal-free media. 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) 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 drug substance manufacturing process is described in great detail, including 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. Conditions for storage of process intermediates have been defined and the maximum time of storage has been specified.

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

The fermentation process (Step 1-3) consists of stepwise expansion of the cell mass.

Overall, acceptable in-process controls are in place throughout the CDP870 manufacturing process. It was however observed that all controls were related to process parameters and not at all to purity improvement during the process. It was recommended that in-process controls for the purity of the CDP870 Fab’ should be introduced before pegylation.

Validation
Originally the validation of the CDP870 drug substance manufacturing process has been performed by analysing parameters of three consecutive full-scale batches through the cell growth, harvest, isolation, pegylation and purification. These studies conducted for validation of the production process were in many respects both well designed and reported, but the control of consistency of the production was addressed only in terms of process performance. No data were reported showing e.g. how product purity progresses in the process of purification, and critical parameters controlling the formation and/or the removal of product related substances/impurities were not identified.
To address this concern, additional studies were performed to evaluate the progression of product purity, the product purity over the defined operation ranges for key process parameters, assessment of the in-process control strategy, review of the criticality of process parameters and considerations of the introduction of additional in-process controls for CDP870 Fab’ purity. Overall, these data indicate that the process is sufficiently validated.

- Characterisation

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.

Although extensive characterisation was done on CDP870 drug substance the use of various different materials, Fab' fragment batches, drug substance batches/drug substance reference standard and the fact that the batches are produced by different processes over a number of years, made it difficult to draw a firm conclusion on the characterisation of CDP870 drug substance.

With the response to the Day 120 LoQ the applicant submitted an exhaustive characterisation of CDP870 Fab' and CDP870 drug substance conducted on material representative of the commercial process, revealing the structure of CDP870 Fab'- and drug substance as well as product related substances and impurities. The methods used are considered as state of the art.

- Specifications

The specifications are justified based on 3 standard deviations around the mean of release data of all batches used in the phase III clinical trials. The end of shelf life specifications are justified based on trend analysis data of stability batches. 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 with the following exception:

Control of purity
An area which is still of major concern is the control of the purity of drug substance and drug product. In the specification originally proposed, the purity tests were solely used to define the maximum levels of specified impurities. Testing of the purity/integrity of the "intact" drug substance was lacking. It was proposed to introduce a specification for the level of purity. The introduction of a SE-HPLC purity test in the specification of the drug substance and drug product had been endorsed, but as no justification was given for choosing this method, it was difficult to conclude whether it was sufficient or not. In order to support the choice of the method, results from other purity tests had therefore been requested.

In order to resolve this issue the applicant, at an oral hearing at the BWP meeting on 9 October 2007, outlined their approach for solving the remaining quality issues.

Considering the orally presented data, the BWP concluded, that the applicant's strategy to resolve this major objection seems adequate. The proposed purity specifications were all based on an acceptable number of batches and they were all shown to be within, or below, the level present in clinical trial material. However, in line with centralised procedures for other medicinal products a final conclusion on this major objection can only be drawn after the assessment of data submitted in writing.

Further at the oral hearing at the BWP on 9 October 2007, the issue on Isomer 1 was addressed by the applicant.

The strategy outlined by the applicant was deemed acceptable to the BWP. Nevertheless, the BWP informed the applicant that an assessment of a written response is required for a final conclusion on this point.

Analytical methods
In general, analytical methods are adequately described. The pre-defined acceptance criteria for each parameter tested are met and it is concluded that the analytical procedures for drug substance release and stability testing have shown to be valid for their intended use.

However, the reports on the validation of the methods used for control of purity (methionine oxidation, CEX-HPLC), SE-HPLC) should be updated to include information on the performance of analysis to quantify the main component and product-related impurities.

Reference standard

The reference material is adequately characterised.

Batch data
Extensive batch analysis data from batches used in phase III clinical studies, for process validation and stability studies have been provided. The data show that the proposed manufacturing process is capable of consistently producing drug substance.

- Stability

Stability data were submitted to justify the proposed shelf life of the drug substance of 24 months 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.

At the time of opinion, the issues relating to the specifications preclude a final conclusion on the stability of the drug substance.

- Comparability Exercise for Drug Substance

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 of the process in an effort to increase the recovery of CDP870 Fab' and to increase the purity of the final CDP870 Drug Substance.

This is from a safety and efficacy point of view, not considered to be of concern as Phase III studies have been conducted with late process material and a further non-clinical study have been conducted with material. Pivotal clinical trials and a non-clinical study have thus been carried out with material representative of the commercial material.

Comparability studies have been performed. The comparability studies consisted of side-by-side comparison of CDP870 drug substance release data, additional analytical characterisation of CDP870 Fab' and CDP870 drug substance together with stability data of the drug substance and finally an evaluation of in-process comparability.
Overall the comparability studies are acceptable and show consistency between materials from the processes.

Medicinal Product

Composition and container closure system
Cimzia drug product is presented as a sterile, white, lyophilisate for solution for subcutaneous injection. Each single dose vial contains 200 mg certolizumab pegol in a 5 mL nominal capacity vial. Each vial is intended for single use, following reconstitution with 1 ml of sterile water for injection (WFI).

The composition of the drug product is listed in the table below.

Names of Ingredients	Unit Dose Quantity	Function	Reference to Quality Standards
CDP870 Drug Substance[a]	200.0 mg	Active Ingredient	Company Standard
Sucrose	100.0 mg	Stabilizer and Bulking Agent	Ph Eur/NF
Polysorbate 20[b]	0.1 mg	Cake Wetting Agent	Ph Eur/NF
Nitrogen	Not Applicable	Processing Aid	NF

[a] Drug Substance Solution contains Lactic Acid (PhEur/USP), This results in the Drug Product containing 0.9mg Lactic Acid per unit dose.
[b] Polysorbate 20 = Tween 20

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.

An overfill is included in the vial to enable withdrawal of 200 mg/mL upon reconstitution.

The reconstitution diluent, sterile Water for Injection, is provided as a 1-mL fill in a 2-mL vial (PhEur) closed with a bromobutyl stopper (PhEur).

- Pharmaceutical Development

The lyophilised 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. Furthermore, a major change in formulation (from liquid formulation to lyophilised formulation) has been introduced. These changes are considered well described and adequate comparability studies have been performed.

- Manufacture of the Product

Manufacturing process
The manufacturing process which was establish based on the experience in development is described in sufficient detail, including information on the control in operation, the compounding, filling and lyophilisation steps. Representative commercial batch formulas for batches of 10,000 and 20,000 vials are provided. The drug product manufacturing process comprises for storage, thawing and pooling of drug substance preparation of excipients solution and compounding of formulated bulk drug product sterile filtration filling and lyophilisation capping and sampling (step 9), storage of lyophilised product, inspection, inkjetting batch number and bulk packaging, shipping, labelling and secondary packaging. The critical steps are defined and controlled.

Studies for validation of the process cover the production of three batches produced in the commercial scale and in accordance with the established batch record. Furthermore, the process was validated.

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.

- Product Specification

In general, the results of the specification analyses show that the manufacturing process used is capable of consistently producing drug product of the required quality. The selected parameters to control the drug product have been adequately justified and are considered acceptable besides those for isomer 1 and control of purity. For the latter one a major concern still remains. Reference is made to the discussion on the drug substance specification above.

With the response to the Day 180 LoI, the applicant proposed the drug product release and end-of-shelf life specifications

Analytical methods
All methods for release testing of the drug product have been adequately described and are validated. The proposed limits are considered acceptable. Regarding the test methods for control of purity reference is made to the discussion on the drug substance specification above.

Batch data
Batch analysis data from 15 batches produced at the commercial manufacturing site confirm the consistency of the drug product manufacture.

- Stability of the Product

The stability of the drug product has been extensively investigated on supportive and commercial batches. The supportive data show that the drug product is stable for the proposed shelf-life of 18 months at 2-8°C. 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.

However, the issues relating to the specifications preclude a final conclusion on the stability of the drug product (reference is made to the section on drug substance specifications and stability).

- Diluent

The composition, manufacture and control of the diluent, Water for Injections in 2 ml glass vials, have been adequately documented. The proposed shelf-life of 36 months when stored at 25 ± 2°C is supported by stability data and is acceptable.

- 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.

The only component used in the commercial manufacture of animal origin is lactose which is derived from bovine milk fit for human consumption. Tryptose has been used in generation of the MCB and was sourced from animals from Austria, Australia, New Zealand, and the United States, countries considered to be free of BSE as of August of 1994 (date of the certificate of analysis for the batch used). Taken the sourcing area and time, and the dilution effect from MCB to fermentation harvest into consideration, the risk of transmitting TSE is considered negligible.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated 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. However, a major concern still remains regarding the control of purity of the drug substance and drug product. Assurance needs to be provided that the quality of the marketed product will be comparable to product on which the marketing authorisation application is based. The

applicant addressed this issue at on oral hearing at the BWP meeting by presenting data for the introduction of additional purity specifications for drug substance and drug product. The BWP considered the applicant's strategy to resolve this major objection as adequate. However, in line with centralised procedures for other medicinal products a final conclusion can only be drawn after the assessment of data submitted in writing. The same conclusion was drawn on the applicant's strategy presented for the clarification on the control of isomer 1 and the submission of updated reports for method validation and stability.

2.3 Non-clinical aspects

Introduction

The conducted non-clinical toxicity studies were all GLP-compliant.

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} 3 ng/ml). It also inhibited 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 IC90 (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. In contrast to other therapeutic TNFα antibodies, e.g. infliximab and adalimumab, certolizumab pegol did not mediate complement-dependent or antibody-dependent cell-mediated cytotoxicity, or induce cell apoptosis. There are no data on e.g. mitogenic effects or interactions with T- or B-cells.

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. No animal model for Crohn's disease has been used.

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

- Secondary pharmacodynamics

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

- Safety pharmacology programme

No *in vivo* safety pharmacology studies were performed. The justification for not undertaking *in vivo* safety pharmacology is accepted.

- Pharmacodynamic drug interactions

No *in vivo* pharmacodynamic drug interaction studies were performed. The justification for not undertaking pharmacodynamic drug interaction studies is accepted.

- Comparability

In vitro, no particular differences were found between materials from different processes, but the analysis criteria have not been validated to detect differences. Two *in vivo* studies were also undertaken. For the mouse model, although no statistical differences were found between the materials or formulations studied, the possibility to pick up small differences in this model is questioned. Results from the rabbit pyrexia model are not clear cut. It appears that material from all processes bound hTNFα in plasma as expected, but that material from process 6, and particularly process 7 had less biological activity than from process 3. Taken together, the available non-clinical data are insufficient to support comparability of material from earlier and later processes during development.

Pharmacokinetics

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 anti-certolizumab pegol antibodies. 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.

In cynomolgus monkeys, certolizumab pegol appeared to have roughly linear pharmacokinetics. Bioavailability appeared 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 $T_{½}$ was 8.5-10.5 days after repeated dosing. The presence of anti-certolizumab pegol antibodies appeared to result in shortened $T_{½}$ values. If antibodies were neutralising remains unknown.

In a distribution study, the PEG component was demonstrated in all analysed tissues (liver, spleen, kidneys, heart, lungs, brain and mesenteric lymph nodes) following administration of certolizumab pegol and the rat equivalent cTN3 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 2x 20 kDa PEG chains linked via a lysine residue. The metabolic fate of the maleimide linker is less clear. Following administration of a single dose of 400 mg/kg certolizumab pegol sc to rats, the terminal $T_{½}$ for PEG was 24 days. The accumulated 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, which was used for testing of reproductive toxicity, showed negligible placental transfer and milk excretion. It was not detected in plasma of nursing pups. cTN3γ1, a complete antibody binding rat TNFα, passed the placenta to some extent (15%), and was excreted in milk (24%).

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 with neutralising anti-certolizumab pegol antibodies did not cross react with infliximab, etanercept or adalimumab.

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 microg/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 fairly 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 related to the certolizumab pegol construct. TNFα is present in a soluble and a transmembrane bound form. If certolizumab pegol binds cells expressing TNFα, it may lead to targeted exposure of certain cells to the PEG component. Data provided support that the majority of cell uptake is not antigen dependent. It was also shown that certolizumab pegol saturated membrane bound TNF α on different cell types from human and cynomolgus monkey, in a similar manner and at concentrations below those achieved in the toxicity studies.

- Single dose toxicity

A slight decrease in T and B-cell marker values and an increase in kidney weight were observed following single iv administration of 100 and 400 mg/kg certolizumab pegol to cynomolgus monkeys.

- 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. A process equivalent to the one intended for marketing (process 7) was applied in the 52-week study while the 26-week study applied certolizumab pegol material from the earlier processes 3 and 4.
No effects on immune function were observed in the 52 weeks study, which is somewhat unexpected for an anti-TNFα agent and in clear contrast to earlier observations with other anti-TNFα agents. Decreases in platelets, white and red blood cells were found in the 52-week study. Increases in PT and 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. It is suggested 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 microg/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.

For assessment of systemic exposure, plasma concentrations are mainly referred to. 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 either.

- Carcinogenicity

Carcinogenicity testing was not performed, which is accepted considering the characteristics of certolizumab pegol. However, in relation to the current knowledge about TNFα in the context of malignancies/lymphoma, there remains a clear concern about long-term suppression of the immune function due to TNFα inhibition and the potential for poorer control of e.g. nascent tumours. There are also signals from the clinical experience with the other anti-TNFα agents.

- Reproduction Toxicity

Reproductive and developmental toxicology was assessed by using a homologous agent; cTN3 PF. It is a chimeric Fab' fragment which is conjugated to 40 kDa PEG. cTN3 PF binds rat TNFα (IC_{90} 1500 ng/ml). Expected pharmacological activity was shown in an arthritis model 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 HD rats. 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. Perhaps the same could be true for certolizumab pegol in humans, although it is unknown.

There are limitations with the testing of reproductive/developmental toxicity. Firstly, only one species was studied. Secondly, only two dose levels were tested and no maternal effects were induced, questioning dose selection. Even if for the high dose group, plasma levels were in considerable excess of IC_{90} for *in vitro* effects, the low dose (20 mg/kg) had minimal or no pharmacological activity in an arthritis disease model, which questions the degree of TNFα inhibition at this dose.

Reproductive/developmental toxicity data for an antibody, which inhibits rodent TNF; cTN3 γ1 were submitted. Administration of this compound resulted in some foetal exposure as well as offspring exposure (via milk). Overall, no effects on female fertility, reproductive function or embryo-foetal and postnatal development were observed. However, male fertility and sperm parameters were not studied.

In conclusion, although 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. The same precautions as for approved anti-TNF agents should be taken.

- Local tolerance

Local tolerance data raised no concern.

- Other toxicity studies

In vitro, certolizumab pegol (acetate buffer) 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. The study report discusses that these effects may be due to the PEG-component based on published experience with other PEGs. Blood compatibility data for the formulation intended for marketing appears to be lacking.

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 fungus. 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).

Ecotoxicity/environmental risk assessment

The environmental risk assessment of certolizumab pegol followed primarily the draft of guidelines related to this issue. From the results obtained, it is concluded that certolizumab pegol for

subcutaneous injection is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

2.4 Clinical aspects

Introduction

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 full pharmacokinetic profile of certolizumab pegol has been characterised only 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 rich data from the healthy volunteer studies, in a population pharmacokinetic (PK) analysis. Several deficiencies have been identified in this population analysis making the confidence in the model low. Thus, results from the analysis have to be interpreted with great caution and, unless the model is re-developed, the information can only be used as indicative of various effects for example evaluation in special populations, time dependency and interactions. A regular multiple-dose PK-study in the target population has not been performed.

The population PK analysis CDP870-039 estimated absolute bioavailability to be 85 %, being in agreement with values obtained in the traditional pharmacokinetic analyses. Mean T_{max} ranged from 54 hours to 171 hours following sc injection. The observed mean C_{max} following 400 mg sc doses ranged from 46.3 ± 13.1 µg/mL to 49.5 ± 8.2 µg/mL. Mean C_{max} increased with increasing doses in an approximately dose-proportional manner. Mean AUC extrapolated to infinity was evaluated following a single 400 mg sc dose ranging from 22,419 ± 7,398 µg.h/mL to 28,752 ± 4,205 µg.h/mL, respectively. AUC increased with increasing dose in a dose-proportional manner. Dose-related exposure has been demonstrated with an approximately linear relationship between the dose administered and the maximum certolizumab pegol concentration (C_{max}) and the area under the certolizumab pegol plasma concentration versus time curve (AUC) in healthy volunteers and patients with Crohn's Disease.
It has not been determined whether injection in either the anterior abdominal wall or the thigh alters the pharmacokinetics. No data are currently available but since the concern arises from a theoretical interference, no further information needs to be obtained for the time being.

The volume of distribution was estimated to be low; around 6 to 7 L for a 70 kg person, similar values obtained in the healthy volunteer studies and in the population PK analysis. Clearance was estimated to approximately 10-15 mL/h in healthy volunteers and a somewhat higher estimate was obtained in the population PK analysis. Certolizumab pegol was found to have a long elimination t1/2 of approximately 14 days. After cessation of treatment plasma concentrations fell to almost minimum detectable levels by week 16.

The potential impact of weight on pharmacokinetics and pharmacodynamics has been evaluated. Even though smaller, expected differences related to bodyweight are observed in the available pharmacokinetic parameters. No effect was found on the pharmacodynamics.

No human data are currently available on the pharmacokinetics of PEG. It is argued that data from preclinical studies in rodents and human data in the literature render it probable that this will also be the case for PEG deriving from certolizumab pegol. A clinical pharmacokinetic study is planned to confirm the route of elimination in humans.

The use of certolizumab pegol will result in the development of antibodies towards the drug in some of the patients. In the pivotal studies of Crohn's disease where subjects received 400 mg sc. (CDP870-031 and CDP870-032) the incidence of subjects testing positive for antibodies at any time during the studies was approximately 8-10%. The proportion of subjects developing antibodies was lower in those receiving concomitant immunosuppressants (3.3%). The fraction of patients developing antibodies seemed to increase-with duration of treatment. It is important to note that the detection of anti-certolizumab pegol 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-certolizumab pegol antibody positive subject is also dependent on the value used as cut-off in the definition.

The presence of antibodies to certolizumab pegol appears to increase the clearance of certolizumab pegol, resulting in a reduction in C_{max}, C_{trough} and AUCτ. This may in turn be important as the drug effect probably will be decreased in these subjects. However, the relation between being an antibody positive patient to the outcome in efficacy and adverse effect is unclear at present.

There appears to be time dependency in the pharmacokinetics for patients being antibody positive and negative. However, the magnitude of the time dependencies and whether its presence may be confounded by the decline in auto-antibodies towards TNFα combined with an unspecific assay for certolizumab pegol remains to be elucidated.

The population analysis did not indicate a strong impact of gender on the pharmacokinetics of certolizumab pegol. Also, available data suggest that there is no effect of age on certolizumab pegol pharmacokinetics. However, few subjects above 70 years were included and no subjects above 73 years of age. Therefore, caution should be exercised in the elderly population.

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 is expected to be renally excreted to a large extent. For the time being, no dosing recommendation in moderate and severe renal impairment can be provided.

The original pharmacokinetic-pharmacodynamic (PK/PD) assessment concluded that doses greater than 400 mg certolizumab pegol may result in some additional improvement in efficacy for induction or up to 12 weeks of treatment, however most of the effect (difference from placebo) would be achieved with a dose of 400 mg. On the basis of data from studies CDP870-031 and CDP870-032 a population PK/PD model was developed in which plasma concentrations of certolizumab pegol was related to the CDAI score. The model was used for clinical trial simulations with other induction dose schemes than the proposed, comprising higher doses or shorter dosing intervals. The results from the simulations indicate that there is no clinical advantage in increasing the initial dosing to 800 mg compared to 400 mg.

- Special populations

No specific studies have been conducted in elderly patients or in patients with liver or renal impairment. However, pharmacokinetics of certolizumab pegol in these populations was investigated in the population PK analysis (see above).

Certolizumab pegol has not been studied in children.

Pharmacodynamics

Certolizumab pegol is an inhibitor of TNFα, a key cytokine that up-regulates cellular adhesion molecules, chemokines and major histocompatibility complex (MHC) class I and class II molecules, as well as directing leukocyte activation. Elevated levels of TNF-α have been implicated in the

pathology of Crohn's disease. TNF-α is strongly expressed in the bowel wall in areas affected by Crohn's disease and faecal concentrations of TNF-α in patients with Crohn's disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn's disease demonstrated a decrease in the levels of the acute phase marker of inflammation, C reactive protein (CRP).

Clinical efficacy

The clinical programme consisted of two dose-finding studies and two pivotal clinical trials. Inclusion criteria in the controlled trials were similar: patients > 18 years of age with Crohn's disease for at least 3 months, a CDAI score between 220 and 450, and no stomas or abscesses. Patients with structuring disease, recent non-inflammatory obstruction or with short bowel were excluded as were patients with gastrointestinal infections and patients who had received prior anti-TNFα therapy without clinical response to first dose or had experienced severe adverse reactions to this. Stable co-medication including in about 40% immunosuppressants and in 20% steroids was allowed and stratified for. The primary efficacy parameter was response defined as a reduction of CDAI of at least 100 or remission (CDAI < 150), respectively lack of increase of the absolute value to more than 175. Remission was a secondary efficacy parameter. Patients were recruited worldwide with the largest subgroup being patients from Eastern Europe. Incomplete data from the two on-going open-label follow-up studies were included in the safety database.

Completed Phase II and Phase III Studies

Protocol	Description of Study	Certolizumab pegol Dose	Number of Subjects Randomized
Phase 2 Safety and Efficacy			
CDP870-005	12-week, multiple dose, parallel group, placebo-controlled, dose-ranging study in subjects with active Crohn's disease (with follow-up to Week 20)	100, 200 and 400 mg sc	219
		Placebo	73
CDP870-008	4-week, single-dose, parallel group, placebo-controlled, dose-ranging study in subjects with active Crohn's disease (with follow-up to Week 12)	1.25, 5, 10 and 20 mg/kg iv	68
		Placebo	24
Phase 3 Safety and Efficacy			
CDP870-031	26-week, multiple dose, parallel group, placebo-controlled, efficacy Phase III study in subjects with active Crohn's disease	400 mg sc	331
		Placebo	329
CDP870-032	26-week, multiple dose, parallel group, placebo-controlled, Phase III study in subjects with active Crohn's disease to assess maintenance of response	400mg sc	216
		Placebo	212

Ongoing Long-term Safety Follow-up Studies

Protocol	Description of Study	Certolizumab pegol Dose	Number of Subjects
Long Term Follow up Safety Studies			

CDP870-033	Open-label safety study in subjects with Crohn's disease for subjects completing –031 or –032. (Dosing up to 2 years)	400 mg sc	595
CDP870-034	Open-label safety study in subjects with Crohn's disease for subjects withdrawing from –031 or –032. (Dosing up to 3 years)	400 mg sc	310

- Dose response studies

Study CDP-870-005 compared placebo with certolizumab pegol 100, 200 and 400 mg sc administered at week 0, 4, and 8. Of 372 patients screened 292 were randomised and 217 remained in the study at week 12 at which time efficacy was assessed. At week 12, the number of patients in each group obtaining response or remission did not differ between groups. Exploratory analyses revealed a statistically significant difference between placebo and 400 certolizumab pegol at week 2, 4, 8, and 10 weeks. The number of patients in remission increased initially in the certolizumab pegol groups and levelled out while the placebo response increased steadily. Further post-hoc, exploratory analysis by baseline CRP levels at entry into the study demonstrated that the difference was confined to patients with initial CRP ≥ 10 mg/L.

The second dose-response, placebo controlled study CDP870-08 was less relevant as only single and intravenous doses were administered. It did not demonstrate efficacy.

- Main studies

Efficacy of certolizumab pegol was compared with placebo as "add-on" therapy in two phase III, multinational, multi-centre, double-blind, parallel group, 26 week placebo controlled studies. They were designed to demonstrate the efficacy of certolizumab pegol to induce (CDP70-031) and maintain (CDP870-032) clinical response in subjects with active Crohn's disease. Clinical remission was a predefined secondary endpoint. The group of patients with baseline CRP ≥ 10 mg/L was the primary efficacy population. The pivotal studies have been published as PRECISE 1 (CDP870-031; NEJM 2007;357:228-38) and PRECISE 2 (CDP870-032; NEJM 2007;357:239-50).

These two studies are presented together because of similarities in the study populations, dose and dose regimens:

METHODS

Study Participants

Study CDP870-031:

The general inclusion criteria were those as described above (introduction to Clinical efficacy). Concomitant medical therapy was allowed including anti-diarrhoeas such as loperamide. Steroid dose should be no more than equivalent to 30 mg prednisolone or 9 mg budenoside and dose should have been stable for 2 weeks and should remain unchanged throughout week 8 after which time tapering was allowed. Steroid was to be tapered by 5 mg/week until 10 mg then by 2.5 mg/week, and budesonide by 3 mg/3 weeks. If exacerbation was entailed during tapering it was allowed to increase once the dose to that given at entry and this dose should be maintained throughout the remainder of the study. Immunnosuppressants were allowed if doses had been stable for at least 8 weeks and duration of treatment at least 4 months. 5-Aminosalicylates and long-term treatment with antibiotics were allowed if dose was stable for 4 weeks prior to randomisation.

A summary of exclusion criteria related to concomitant therapy is given hereafter:

Exclusion Criteria for Class of Drug for Crohn's disease in Study CDP870-031

Drug Class	Exclusion Criteria
Corticosteroid/Corticotrophin	• Any therapy for indication other than Crohn's disease except for topical hydrocortisone for skin disease or ≤ 800 µg/day inhaled beclomethasone, or equivalent, for asthma • Parenteral therapy within 4 weeks of screening • Discontinuation within 2 weeks of screening
Azathioprine, 6-mercaptopurine, methotrexate, chronic (>4 weeks) antibiotic therapy	• Discontinuation within 4 weeks of screening
Cyclosporin, mycophenolate, thalidomide	• Regular treatment for Crohn's disease within 4 weeks of screening

Previous treatment with anti-TNF therapy other than certolizumab pegol was allowed unless the subject had had a severe hypersensitivity or anaphylactic reaction or had no clinical response to the first dose. Subjects who had received any biological therapies (within or outside of clinical studies) within 12 weeks prior to screening or were dosed in any clinical study within 4 weeks prior to screening were excluded.

Other exclusion criteria were based on safety parameters such as chronic infections including a history of tuberculosis, concurrent malignancy, history of lymphoproliferative disorders, or uncontrolled systemic disease.

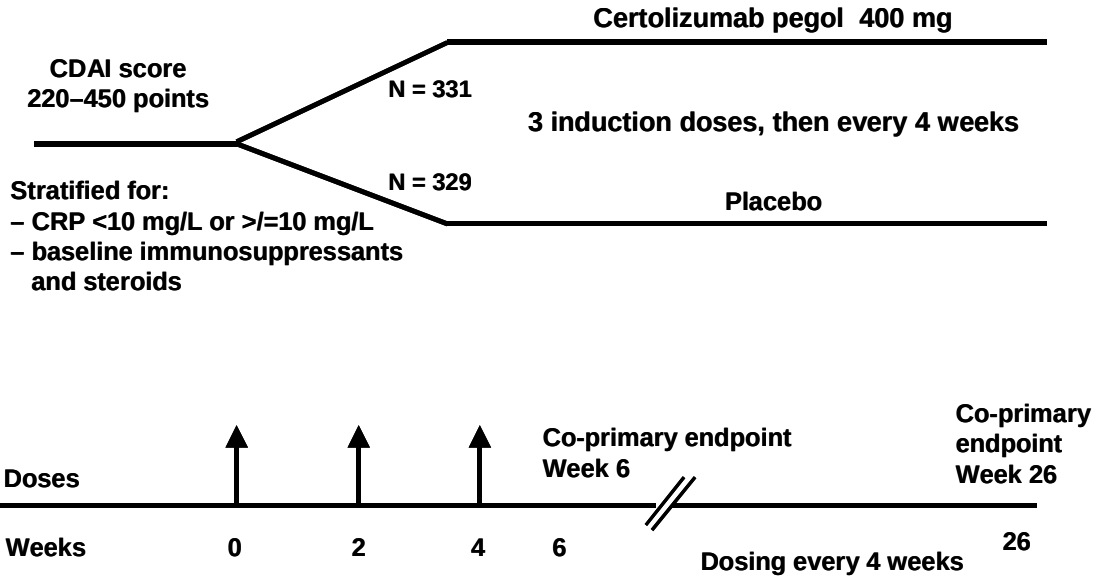
Study CDP870-032: Except that all patients in this study received three doses of open label certolizumab, and thereafter were randomised to either placebo or certolizumab, the design was as for study CDP870-031; including identical initial recruitment criteria as in study CDP870-031. Patients not completing the study were followed up by telephone 12 weeks after the last dose of study drug. No major protocol amendments were made.

For both trials, subjects were stratified at randomisation by three factors:
- CRP <10 mg/L or ≥10 mg/L at study entry
- Receiving corticosteroids at study entry or not
- Receiving immunosuppressants at study entry or not

Treatments and randomisation

Study CDP870-031

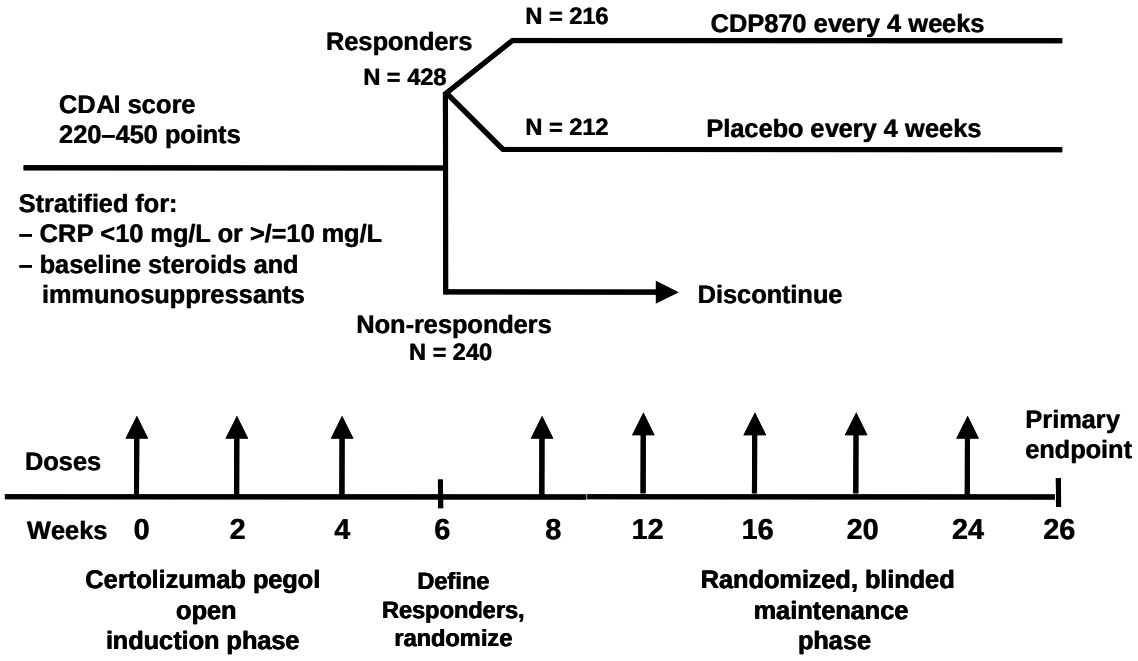
Eligible subjects were randomized in a 1:1 ratio to receive either placebo or 400 mg certolizumab pegol administered subcutaneously at Weeks 0, 2, 4, and then every 4 weeks at Weeks 8, 12, 16, 20, and 24.



A final study visit was scheduled at Week 26 for safety and efficacy evaluation. Blood samples were taken at each study visit, prior to receiving certolizumab pegol on dosing visits, to measure certolizumab pegol plasma concentration and anti-certolizumab pegol antibodies.

Study CDP870-032

Patients demonstrating clinical response to subcutaneous injections of Certolizumab 400 mg at weeks 0, 2, 4 were randomised at week 6 to either continued injections of Certolizumab 400 mg or placebo every four weeks from week 8 through week 24.



Endpoints

Study CDP870-031

The co-primary endpoints were the percentage of subjects with clinical response at Week 6 and at both Weeks 6 and 26 in the strata defined by CRP ≥10 mg/l at Baseline. Secondary efficacy endpoints included assessment of clinical remission at Week 6 and at both Weeks 6 and 26 in subjects with Baseline CRP ≥10 mg/l, assessment of clinical response and remission irrespective of Baseline CRP levels (i.e., in the Overall population), percentage of subjects with IBDQ response at Week 6 and at both Weeks 6 and 26, and SF-36 sub-scores and change from baseline in SF-36 sub-scores for bodily pain and role physical at Weeks 6, 16, and 26 (Quality of Life measurements). Clinical response was also recorded using HBI for subsequent analysis of long-term response in subjects who continued into the safety studies, CDP870-033 and CDP870-034.

Study CDP870-032

The primary endpoint was the proportion of patients remaining in clinical response at week 26 in patients with CRP ≥ 10 mg/l at baseline, week 0. Major secondary endpoints in the high CRP stratum were (a) time to disease progression defined as either an increase in CDAI > 100 above the value at week 6, or an absolute CDAI ≥ 175 at two consecutive visits at least 2 weeks apart, or the use of rescue therapy (steroids or immunosuppressants in individuals not on this therapy at baseline, use of infliximab, surgery or hospitalisation); (b) proportion in clinical remission at week 26; (c) proportion with IBDQ response > 16 points at week 26. Estimates of all four endpoints in the entire ITT population were other secondary end points.

Sample size

Study CDP870-031

For clinical response at week 6, a placebo response of 30% and a clinically relevant difference between treatments of 25% was decided. For the week 6+26 endpoint a placebo response of 15% and a minimal clinically relevant difference of 15% were used. A two-sided level of significance of 5% and a power of 85% were used. The number of patients needed in each treatment arm was calculated to be 151. Since this number of participants was wanted in each arm of the two CRP strata a total number 604 patients were to be randomised. An additional 30% were to be screened (total 1006) to allow for screening failure.

Study CDP870-032

A placebo response rate of 25% at week 26 was assumed and a difference of 20% considered clinically relevant. With a level of statistical significance of 0.05 and a power of 80% for a two-sided test 98 patients in each arm was needed. Since this number was needed in both CRP strata giving four arms and a response rate of 55% during the initial open treatment period was expected a total of 712 patients were to be included in the initial phase. It was estimated that 1186 patients were to be screened.

*Blinding (masking) –**for both studies***

The active treatment and placebo matched in colour and viscosity. Blinding was maintained through the 26 weeks and no interim analysis performed.

*Statistical methods – **for both studies***

Analysis was intention to treat. Analysis of primary efficacy parameter was logistical regression with factors for study treatment, steroid use at entry, use of immunosuppressants at entry and country or region. Tests were two-sided. Withdrawn patients were considered therapeutic failures. The interaction between treatment and subgroups was tested

RESULTS

Participant flow

A total of 976 patients were screened for participation in CDP70-031 and 662 were randomised. Among those, 660 received treatment since one patient was erroneously included into a stratum to which recruitment was already completed and one declined further participation.

Of the 930 patients screened in CDP70-032, 262 were screening failures, 668 subjects received open label treatment. Among them, 240 were non-responders and 428 (64.1%) were in clinical response at Week 6 and received at least one double-blind treatment after randomization. Of these 428 responders at Week 6, 425 were included in the Overall ITT population for analysis of efficacy. Three subjects from one site were excluded because of potential un-blinding to treatment assignment.

Baseline characteristics are given in the following tables:

Demographics and Baseline Characteristics of Overall ITT Population in Studies CDP870-031 and CDP870-032

	CDP870-031 (Randomized Treatment)		**CDP870-032 (Randomized Withdrawal)**	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Number of subjects randomized	328	331	210	215
Age (years)				
n	328	331	210	215
Mean (± SD)	37.9 ± 12.0	36.8 ± 11.8	37.6 ± 12.1	37.5 ± 11.2
Median	36.5	36.0	36.0	36.0
Min., Max.	18, 77	18, 73	18, 69	18, 67
Gender				
Male	131 (39.9%)	157 (47.4%)	109 (51.9%)	92 (42.8%)
Female	197 (60.1%)	174 (52.6%)	101 (48.1%)	123 (57.2%)
Race				
Caucasian	313 (95.4%)	313 (94.6%)	191 (91.0%)	202 (94.0%)
Afro-Caribbean	0	5 (1.5%)	3 (1.4%)	2 (0.9%)
Asian (Indian)	1 (0.3%)	2 (0.6%)	4 (1.9%)	6 (2.8%)
Asian (Oriental)	2 (0.6%)	2 (0.6%)	1 (0.5%)	1 (0.5%)
American Indian	0	0	1 (0.5%)	0
Other	12 (3.7%)	9 (2.7%)	10 (4/8%)	4 (1.9%)
Height (m)				
n	328	331	210	215
Mean (± SD)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Median	1.7	1.7	1.7	1.7
Min., Max.	1.5, 1.9	1.5, 2.0	1.5, 2.0	1.5, 2.0
Weight (kg)				
n	328	329	210	215

	CDP870-031 (Randomized Treatment)		CDP870-032 (Randomized Withdrawal)	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Mean (± SD)	68.6 ± 17.7	68.7 ± 17.15	72.1 ± 17.4	68.7 ± 16.7
Median	66.0	66.1	67.9	66.4
Min., Max	38.4, 150.0	37.0, 148.6	43.5, 136.4	33.3, 136.0
Body Mass Index (kg/m^2)				
n	328	329	210	215
Mean (± SD)	23.8 ± 5.3	23.8 ± 5.4	24.5 ± 5.5	23.7 ± 5.3
Median	22.7	22.7	23.1	22.9
Min., Max	14.7, 53.0	13.2, 45.4	15.7, 45.4	13.5, 56.7
Smoking				
Never	149 (45.4%)	156 (47.1%)	98 (46.7%)	91 (42.3%)
Stopped before CD diagnosis	37 (11.3%)	32 (9.7%)	15 (7.1%)	18 (8.4%)
Stopped after CD diagnosis	35 (10.7%)	39 (11.8%)	21 (10.0%)	42 (19.5%)
Current Smoker	107 (32.6%)	104 (31.4%)	76 (36.2%)	64 (29.8%)
Geographic locations				
North America	63 (19.2%)	76 (23.0%)	61 (29.1%)	48 (22.3%)
Western Europe	54 (16.4%)	50 (15.1%)	36 (17.1%)	46 (21.4%)
Eastern Europe	157 (47.9%)	156 (47.1%)	64 (30.5%)	66 (30.7%)
Rest of the World	54 (16.5%)	49 (14.8%)	49 (23.3%)	55 (25.6%)

Summary of History of Crohn's Disease in Overall ITT Population in Studies CDP870-031 and CDP870-032

	CDP870-031 (Randomized Treatment)		CDP870-032 (Randomized Withdrawal)	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Number in Overall ITT Population	328	331	210	215
Baseline CDAI Score				
N	327	329	209	215
Mean (± SD)	297 ± 62	300 ± 64	301 ± 61	306 ± 61
Median	285.2	287.7	287.3	296.5
Min., Max.	161, 513	149, 491	183, 583	179, 504

	CDP870-031 (Randomized Treatment)		CDP870-032 (Randomized Withdrawal)	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Duration of Crohn's disease (years)				
N	327	331	210	215
Mean (± SD)	7.7 ± 7.3	7.2 ± 7.7	7.3 ± 7.8	8.6 ± 7.1
Median	5.5	4.8	4.5	6.7
Min., Max.	0.2, 40.2	0.3, 43.8	0.3, 42.8	0.3, 32.7
Location of Crohn's disease				
Terminal Ileum	82 (25.0%)	91 (27.5%)	49 (23.3%)	45 (20.9%)
Colon	71 (21.6%)	87 (26.3%)	57 (27.1%)	56 (26.0%)
Ileocolon	158 (48.2%)	138 (41.7%)	89 (42.4%)	104 (48.4%)
Upper GI	17 (5.2%)	15 (4.5%)	15 (7.1%)	10 (4.7%)
Resections				
Yes	113 (34.5%)	118 (35.6%)	73 (34.8%)	64 (29.8%)
No	215 (65.5%)	213 (64.4%)	137 (65.2%)	151 (70.2%)
Number of Resections				
0	215 (65.5%)	213 (64.4%)	137 (65.2%)	151 (70.2%)
1	76 (23.2%)	79 (23.9%)	49 (23.3%)	45 (20.9%)
2	28 (8.5%)	25 (7.6%)	13 (6.2%)	12 (5.6%)
3	6 (1.8%)	8 (2.4%)	7 (3.3%)	3 (1.4%)
>3	3 (0.9%)	6 (1.8%)	4 (1.9%)	4 (1.9%)

Summary of Previous Infliximab and Baseline Corticosteroid and Immunosuppressant Use in Studies CDP870-031 and CDP870-032

	CDP870-031 (Randomized Treatment)		CDP870-032 (Randomized Withdrawal)	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Number in Overall ITT Population	328	331	210	215
Previous infliximab	85 (25.9%)	100 (32.2%)	51 (24.3%)	52 (24.2%)
Baseline corticosteroids and immunosuppressants				
Corticosteroids only	75 (22.9%)	72 (21.8%)	44 (21.0%)	47 (21.9%)
Immunosuppressants only	66 (20.1%)	69 (20.8%)	52 (24.8%)	59 (27.4%)

	CDP870-031 (Randomized Treatment)		CDP870-032 (Randomized Withdrawal)	
	Placebo	**Certolizumab pegol 400mg**	**Placebo**	**Certolizumab pegol 400mg**
Corticosteroids and Immunosuppressants	55 (16.8%)	57 (17.2%)	34 (16.2%)	28 (13.0%)
Neither	132 (40.2%)	133 (40.2%)	80 (38.1%)	81 (37.7%)

Results

The main results for ***study CDP870-031*** are shown below.

Clinical Response in total ITT and CRP ≥ 10 mg/L Populations

	ITT Population		CRP ≥ 10 mg/L	
	Placebo (N=328)	**Certolizumab (N=331)**	**Placebo (N=156)**	**Certolizumab (N=146)**
Week 6				
n	325	327	154	145
Responded	87	115	40	54
%	26.8%	35.2%	26.0%	37.2%
(95% CI)	(22.0%, 31.8%)	(30.0%, 40.3%)	(19.0%, 32.9%)	(29.4%, 45.1%)
Odds Ratio		1.51		1.70
(95% CI)		(1.08, 2.11)		(1.03, 2.80)
p-value (a)		0.016		0.037
Week 26				
n	327	328	156	145
Responded	87	122	30	47
%	26.6%	37.2%	19.2%	32.4%
(95% CI)	(21.8%, 31.4%)	(32.0%, 42.4%)	(13.0%, 25.4%)	(24.8%, 40.0%)
Odds Ratio		1.64		1.97 (1.16, 3.37)
(95% CI)		(1.17, 2.30)		0.013
p-value (a)		0.004		
Weeks 6 and 26				
n	325	325	154	144
Responded	52	75	19	31
%	16.0%	23.1%	12.3%	21.5%

(95% CI)	(12.0%, 20.0%)	(18.5%, 27.7%)	(7.1%, 17.5%)	(14.8%, 28.2%)
Odds Ratio (95% CI) p-value (a)		1.58 (1.06, 2.35) 0.024		1.91 (1.02, 3.57) 0.045
Δ CDAI				
Week 6	-63 (-325, 250)	-73 (-321, 263)	-62 (-325, 250)	-78 (-321, 263)
Week 26	-107 (-348, 123)	-125 (-366, 80)	-76 (-340, 59)	-135 (-366, 76)

p-values were calculated using logistic regression with factors for treatment, CRP strata, corticosteroid use at entry, immunosuppressant use at entry and geographical region.

Median changes (range) in CDAI score from baseline differed only slightly between treatment groups further stressing the small differences and the likely large number of patients included with mild disease.

The following Table shows the results for remission throughout the study period.

Remission by study visit in CDP870-031

	No Previous Infliximab		**Overall Population**	
	Placebo (N=243)	**CDP870 400 mg (N=231)**	**Placebo (N=328)**	**CDP870 400 mg (N=331)**
Week 2	n=242 21 (8.7%)	n=231 35 (15.2%)	n=327 27 (8.3%)	n=330 43 (13.0%)
Odds Ratio (95% CI)		1.86 (1.04, 3.32)		1.70 (1.02, 2.84)
Week 4	n=242 25 (10.3%)	n=230 48 (20.9%)	n=327 37 (11.3%)	n=329 63 (19.1%)
Odds Ratio (95% CI)		2.31 (1.36, 3.92)		1.88 (1.21, 2.94)
Week 6	n=241 46 (19.1%)	n=230 56 (24.3%)	n=326 57 (17.5%)	n=329 71 (21.6%)
Odds Ratio (95% CI)		1.36 (0.87, 2.12)		1.31 (0.89, 1.94)
Week 8	n=241 49 (20.3%)	n=230 65 (28.3%)	n=326 62 (19.0%)	n=330 80 (24.2%)
Odds Ratio (95% CI)		1.55 (1.01, 2.39)		1.36 (0.93, 1.98)
Week 12	n=242 51 (21.1%)	n=230 72 (31.3%)	n=327 65 (19.9%)	n=328 90 (27.4%)
Odds Ratio (95% CI)		1.69 (1.11, 2.58)		1.54 (1.06, 2.22)
Week 16	n=243 54 (22.2%)	n=230 69 (30.0%)	n=328 66 (20.1%)	n=329 87 (26.4%)
Odds Ratio (95% CI)		1.48 (0.97, 2.25)		1.42 (0.98. 2.06)
Week 20	n=243 49 (20.2%)	n=226 61 (27.0%)	n=328 62 (18.9%)	n=325 76 (23.4%)
Odds Ratio (95% CI)		1.46 (0.94, 2.25)		1.31 (0.89, 1.92)
Week 24	n=243 48 (19.8%)	n=230 71 (30.9%)	n=328 60 (18.3%)	n=330 87 (26.4%)
Odds Ratio (95% CI)		1.80 (1.17, 2.76)		1.62 (1.11, 2.35)
Week 26	n=243	n=230	n=328	n=329

	49 (20.2%)	78 (33.9%)	60 (18.3%)	97 (29.5%)
Odds Ratio (95% CI)		2.03 (1.33, 3.10)		1.90 (1.31, 2.76)

With respect to assessment of effect on induction treatment, the rate of remission at week 6 (primary endpoint) was not significantly different between groups. The observed difference between placebo and active treatment was 4.1%. Together with the modest, although statistically significant, effect on response at week 6 (observed difference of < 9%), these data severely questions the clinical relevance of the demonstrated difference between certolizumab and placebo with regard to induction treatment.

For study ***CDP870-032*****,** the main results were as follows:

Clinical Response in Overall ITT and CRP ≥ 10 mg/L Populations

	ITT Population		**CRP ≥ 10 mg/L**	
	Placebo (N=210)	**Certolizumab (N=215)**	**Placebo (N=101)**	**Certolizumab (N=112)**
Week 6 (open phase)				
n	208	215	99	112
Responded	198	203	96	108
%	95.2%	94.4%	97.0%	96.4%
(95% CI)	(92.3%, 98.1%)	(91.4%, 97.5%)	(93.0%, 99.8%)	(93.0%, 99.9%)
Week 26				
n	210	215	101	112
Responded	76	135	34	69
%	36.2%	62.8%	33.7%	61.6%
(95% CI)	(29.7%, 42.7%)	(56.3%, 69.3%)	(24.4%, 42.9%)	(52.6%, 70.6%)
Odds Ratio		3.12		3.30
(95% CI)		(2.07, 4.69)		(1.83, 5.97)
p-value (a)		<0.001		<0.001
Weeks 6 and 26				
n	208	215	99	112
Responded	72	129	31	66
%	34.6%	60.0%	31.3%	58.9%
(95% CI)	(28.2%, 41.1%)	(53.5%, 66.5%)	(22.2%, 40.4%)	(49.8%, 68.0%)
Odds Ratio		3.01		3.40
(95% CI)		(2.00, 4.54)		(1.86, 6.20)
p-value (a)		<0.001		<0.001

(a) p-values were calculated using logistic regression with factors for treatment, CRP strata, corticosteroid use at entry, immunosuppressant use at entry and geographical region.

Response rates for both treatments at week 6 were higher than in study CDP870-031 as would be expected for an open label study. The loss of response was faster in the placebo group and the difference similar in both the high CRP stratum and in the total ITT population. The Kaplan-Meier

plot also demonstrated a difference in the probability for disease progression in favour of certolizumab.

The results for **maintenance of remission** were similar with a significant effect of certolizumab.

Remission at Week 26 in CDP870-031 and CDP870-032

	No Previous Infliximab		**Overall Population**	
Study CDP870-031	Placebo (N=243)	CDP870 (N=230)	Placebo (N=328)	CDP870 (N=331)
Week 26	n=243 49 (20.2%)	n=230 78 (33.9%)	n=328 60 (18.3%)	n=329 97 (29.5%)
Odds Ratio (95% CI)		2.03 (1.33, 3.10)		1.90 (1.31, 2.76)
Study CDP870-032	Placebo (N=159)	CDP870 (N=163)	Placebo (N=210)	CDP870 (N=215)
Week 26	n=159 53 (33.3%)	n=163 86 (52.8%)	n=210 60 (28.6%)	n=215 103 (47.9%)
Odds Ratio (95% CI)		2.26 (1.42, 3.60)		2.44 (1.61, 3.70)

To conclude, the increment in remission at week 26 obtained with certolizumab in CDP870-032 is significant and clinically relevant, although the magnitude of effect cannot be assessed in this trial, due to its enrichment design. However, the efficacy demonstrated in CDP870-031 is not convincing, and there is thus not sufficient support for induction treatment.

Ancillary analyses

Sensitivity analyses were performed for both pivotal studies and demonstrated a higher response rate with certolizumab than with placebo.

A total of 83 subjects in study CDP870-031 and 50 subjects in study CDP870-032 had neither received steroids nor immunosuppressants prior to inclusion. Less than 40% received immunosuppressants and approximately one third had never been on immunosuppressants. Thus treatment of a significant number of patients was not optimised before entry into the studies, and they were not truly refractory to these agents. The low rate of treatment with immunosuppressants is particularly worrisome as this is state of the art in Crohn's disease patients with persistent or recurrent inflammatory activity. The response rate to certolizumab was higher in those receiving concomitant steroids or immunosuppressants in comparison with those who had previously received these agents possibly indicating a steroid sparing effect of certolizumab, or a less treatment resistant population. This notion cannot be examined further in the studies in which steroid tapering was allowed at the discretion of the investigator. The subgroup analysis did not provide data on treatment naïve patients.

In the higher CRP strata, response rates were higher with certolizumab whereas the rates of remission were lower, while for the placebo group, the response rates were similar and rates of remission lower. With respect to induction and maintenance of remission, the efficacy of certolizumab was only slightly higher than with placebo. By contrast, efficacy tended to be lower with more severe disease whether defined by high CRP or by classification as penetrating disease.

A comparison of remission obtained at week 4 (at which time the placebo effect was particularly low in study CDP870-005) with other approved anti-TNFα therapies, in particular infliximab was performed:

Summary of remission data at week 4 for certolizumab, infliximab and adalimumab.

Remission at week 4	***Pl***	***Active***
CDP870-005	*8.2% (6/73)*	*22.2% (16/72)*
CDP870-031	*11.3% (37/327)*	*19.1% (63/329)*
Infliximab	*4% (1/24)*	*48% (13/27)*
Adalimumab, 80/40 mg	*12% (9/74)*	*24% (18/75)*
Adalimumab, 160/80 mg	*12%*	*36% (27/76)*

- Other supportive studies

Long term efficacy data were obtained from the open extension study ***CDP870-033*** to which patients from the pivotal studies qualified at week 26 given they had received active treatment with certolizumab and obtained response or remission. Patients were given certolizumab 400 mg every four weeks for up to 152 weeks. An interim report includes data on all patients through 12 months of treatment. A total of 595 of 1084 patients entering the pivotal studies entered CDP870-033 and 391 completed at least 12 months treatment. The interim analysis gives data on patients randomised to certolizumab in the pivotal studies only, n = 331 (from CDP870-031) + 215 (from CDP870-032) = 546, of whom 250 appears to have entered CDP870-033. Withdrawal rate in CDP870-033 was 34% and mostly due to increase in disease activity.

Study CDP870-033 used the validated Harvey Bradshaw Index (HBI) as measure of disease activity. A reduction of CDAI of 100 points corresponded to a decrease in HBI score of 3.28 points and remission (CDAI > 150) to a HBI of 4.46. A reduction of HBI of ≤ 3 points from baseline HBI at entry into the qualifying study was defined as the HBI response and an absolute score of ≤ 4 points or less in the HBI scale was defined as remission.

The results of the interim analysis for the overall ITT population were:

	HBI response	
	CDP870-031	CDP870-032
Time points from start of 031 or 032	Certolizumab N=331	Certolizumab N=215
Week 26	129 (39%)	121 (56%)
Week 52	103 (31%)	97 (45%)
Week 80	94 (28%)	86 (40%)

	HBI remission	
	CDP870-031	CDP870-032
Time points from start of 031 or 032	Certolizumab N=331	Certolizumab N=215
Week 26	88 (27%)	103 (48%)
Week 52	80 (24%)	88 (41%)
Week 80	76 (23%)	78 (36%)

The long term efficacy data from study CDP870-033 were obtained in an open uncontrolled study. The dropout rate was high, and the data suggest a decline of the effect with time. While the efficacy data for long term maintenance of remission do not suffice, the study provided relevant safety data.

- Effect of anti-certolizumab antibodies

In (Studies CDP870-031 and CDP870-032), the overall percentage of antibody-positive subjects was (8%) in subjects continuously exposed to certolizumab pegol. Antibody generation was lower in those using concomitant immunosuppressants (3.3% across both studies) compared to those who were not

(11.2% across both studies) but was similar, irrespective of corticosteroid use (7.4% and 8.5% across both studies for those using and not using concomitant corticosteroids, respectively). Concerning the development of anti-certoluzimab- antibodies, there seems to be no impact of prior anti-TNFα therapy.

Among subjects who were antibody positive (cut-off value of 2.4 units/ml), approximately 80% had antibodies with neutralizing activity.

No difference could be seen in the percentage of responders in the certolizumab treatment group between antibody positive and antibody negative populations. This finding is maintained even when the cut-off is lowered to 0.6 units/ml

- Discussion on clinical efficacy

Although generally acceptable and clinically relevant, the methods used and the criteria for inclusion in the pivotal trials were problematic. Some patients were included without a prior course of steroids and/or immunosuppressants of sufficient dose and duration to justify the labelling of "add-on" therapy. In addition, the stratification for CRP level was decided based on study CDP870-005 in which the different outcome related to CRP level was detected in a post-hoc exploratory analysis. The CRP level has been shown to correlate with the CDAI score and to signs and markers of disease activity, including findings at endoscopy and radiology. CRP correlated to mild to moderate disease activity but not to severe activity and Odds-ratio for any disease activity provided in one study was only 2 (0.7-7.0). In relation to the design of the pivotal studies, the point is that normal CRP does not rule out even severe activity and CRP is a non-specific marker of inflammation. These facts are the most probable explanation why the association found in the phase II study was not apparent in the pivotal studies. It is acknowledged that the study had the power for analysis of both populations and the results for the total ITT population and the high CRP level subgroup are similar.

With respect to assessment of effect on induction treatment in study 031, the rate of remission at week 6 (primary endpoint) was not significantly different between groups. The observed difference between placebo and active treatment was 4.1%. Together with the modest, although statistically significant, effect on response at week 6 (observed difference of < 9%), these data do not support demonstration of clinical relevance.

No subgroup of patients with Crohn's disease was identified with a particular effect of certolizumab. Clinical effect and differences between treatments were less in patients with prior usage of infliximab and not statistically significant. The results were robust, but the clinical relevance unclear, and the blinded observation period too short for the indication of long-term maintenance of remission. Furthermore, the positive effect of maintenance treatment only indicates that it is beneficial with prolonged treatment in subjects responding to therapy in the first 6 weeks. One further major problem with the maintenance studies is the lack of placebo control after week 26. The 'Points to consider' document clearly recommends that the primary endpoint for maintenance treatment should be maintenance of remission throughout 12 months. Controlled results for maintenance treatment over 12 months were previously obtained for other anti-TNF agents, indicated for treatment of Crohn's Disease. The open extension study does not suffice for this, and thus no sufficient evidence of long term efficacy has been provided.

Sustained remission throughout the study period is the most robust and clinically relevant parameter. An effect is demonstrated in CDP870-032 in a selected population while the treatment effect on remission in week 6 and week 26 in CDP870-031 is small and clinically not relevant.

CDP870-031	Remission Week 6 and 26	Placebo n=326 32 (9.8%)	CDP870 n=327 47 (14.4%)

Since an effect on maintenance is only beneficial in subjects demonstrating response to open label induction therapy in the first 6 weeks at which time the efficacy in terms of remission is not considered clinically relevant based on results from study 031, where magnitude of effect can be assessed, the data are difficult to interpret and even more difficult to translate into a treatment algorithm.

Although efficacy is not readily comparable between different anti-TNFα agents due to difference with regards to study design and definitions of response, the observed differences between placebo and active treatment for the approved anti-TNFα agents in this indication appear more robust than the results for certoluzimab, particularly for induction treatment.

Clinical safety

- Patient exposure

The main data are those derived from the randomized, placebo-controlled studies in patients with Crohn's disease and the open follow-up studies CDP870-033 and 034. Supportive data stem from open studies, studies in healthy volunteers and studies in rheumatoid arthritis. The number of patients exposed to any certolizumab dose was 3654. The safety base included more than 600 Crohn's disease patients treated with certolizumab for one year and more than 300 treated for up to two years. Placebo exposure was 26 weeks at most. The serious adverse events database includes all reports up to 31.12.2006 for all indications.

Patients were considered as being to be exposed for 28 days after the last dose. The pooled Crohn's disease population included 1564 unique subjects. A total of 611 subjects were exposed to certolizumab for at least one year. The estimated patient year exposure was almost 10-fold longer for certolizumab (1379 patient years) than for placebo (142 patient years).

Table 2.7.4:4 Summary of Subject Exposure: Crohn's Disease Pooled Population

	Placebo (N=426)		CDP870 400 mg (N=1350)		All CDP870 Doses (N=1564)	
Exposure (pt-yrs)	139.24		1165.02		1200.33	
Number of doses received						
Mean (SD)	5.0	(2.79)	12.4	(8.73)	11.0	(8.85)
Median	4.0		11.0		8.0	
Range	1-8		1-32		1-32	
Duration of continuous exposure (days)						
Mean (SD)	119.4	(72.64)	315.2	(239.87)	280.3	(239.66)
Median	88.5		279.5		178.0	
Range	6-263		28-887		28-887	
Cumulative duration of continuous dosing						
Any exposure	426	(100.0%)	1350	(100.0%)	1564	(100.0%)
≥ 2weeks	420	(98.6%)	1350	(100.0%)	1564	(100.0%)
≥4 weeks	404	(94.8%)	1350	(100.0%)	1564	(100.0%)
≥2 months	289	(67.8%)	1016	(75.3%)	1130	(72.3%)
≥4 months	196	(46.0%)	861	(63.8%)	861	(55.1%)
≥6 months	177	(41.5%)	779	(57.7%)	779	(49.8%)
≥9 months	0		681	(50.4%)	681	(43.5%)
≥12 months	0		611	(45.3%)	611	(39.1%)
≥18 months	0		315	(23.3%)	315	(20.1%)
≥24 months	0		37	(2.7%)	37	(2.4%)

CDP870 = certolizumab pegol; SD=standard deviation; pt-yers=patient-years
Source: ISS Table 7.1:1, ISS Table 7.1:3 (Module 5, Section 5.3.5.3.3.2), Supplementary Safety Table 1.1:1, Supplementary Safety Table 1.1:2 (Module 5, Section 5.3.5.3.3.4)

Table 2.7.4:5 Estimated Number of Subjects and Patient-Years: Crohn's Disease Pooled and Non-Pooled Studies

CDP870 (all doses)[a]		Placebo	
Number of unique subjects	Number of patient-years	Number of unique subjects	Number of patient-years
1630	1379.30	447	141.96

CDP870 = certolizumab pegol
[a] All subjects from CDP987-032 have been allocated to the certolizumab pegol group.
Source: Supplementary Safety Table 2.1:5, Supplementary Safety Table 2.1:6 (Module 5, Section 5.3.5.3.3.4)

Subject disposition for Crohn's disease was as shown in the table below.

Table 2.7.4:9 Summary of Subject Disposition: Crohn's Disease Pooled Population

	Placebo (N=426)		CDP870 400 mg (N=1350)		All CDP870 Doses (N=1564)	
Commenced at least one study	426		1350		1564	
Ongoing in Study CDP870-033 or CDP870-034 at cut-off[a]	0		522	(38.7%)	522	(33.4%)
Completed at least one study	250	(58.7%)	513	(38.0%)	665	(42.5%)
Withdrawn from at least one study	179	(42.0%)	829	(61.4%)	891	(57.0%)
Reason for withdrawal:						
Adverse event	48	(11.3%)	331	(24.5%)	349	(22.3%)
Non-compliance	2	(0.5%)	22	(1.6%)	22	(1.4%)
Subject decision	16	(3.8%)	191	(14.1%)	206	(13.2%)
Clinical decision	22	(5.2%)	105	(7.8%)	115	(7.4%)
Lost to follow up	0		22	(1.6%)	23	(1.5%)
Lack of efficacy	133	(31.2%)	473	(35.0%)	520	(33.2%)
Other	7	(1.6%)	52	(3.9%)	52	(3.3%)

CDP870 = certolizumab pegol
Note: Data displayed as number of subjects (% of subjects).
Subjects may have withdrawn from a study for more than one reason and in addition, may have completed or withdrawn from more than one study. Subjects have been counted only once in each reason category for each relevant treatment.
[a] Cut-off dates 16-Jun-2006 for CDP870-033 and 28-Mar-2006 for CDP870-034.
Source: ISS Table 2.1:1 (Module 5, Section 5.3.5.3.3.2)

- Adverse events

All adverse events were treatment emergent including events that worsened since baseline.

Table 2.7.4:21 Overall Summary of Treatment-Emergent Adverse Events, Number of Events (Number of Subjects, % of Subjects): Crohn's Disease Pooled Population

	Placebo (N=426)		CDP870 400 mg (N=1350)		All CDP870 Doses (N=1564)	
Any AE	1423	(327, 76.8%)	7413	(1125, 83.3%)	8191	(1286, 82.2%)
Intensity[a]						
Mild	743	(249, 58.5%)	4012	(899, 66.6%)	4379	(1022, 65.3%)
Moderate	537	(217, 50.9%)	2890	(819, 60.7%)	3192	(933, 59.7%)
Severe	143	(67, 15.7%)	511	(286, 21.2%)	620	(337, 21.5%)
Related to study drug[b]	437	(165, 38.7%)	1671	(545, 40.4%)	2034	(654, 41.8%)

AE=Adverse event; CDP870 = certolizumab pegol
Data displayed as number of events (number of subjects, % of subjects).
[a] Based on report of at least one AE in the respective intensity category. Missing severity was counted as severe. Maximum severity is presented.
[b] Includes possible, probably, or definitely related; missing relationship was counted as related. Maximum relationship is presented.
Source: ISS Table 8.1:1 Module 5, Section 5.3.5.3.3.2

The majority of adverse events were mild to moderate.

The most common adverse event was exacerbation of Crohn's disease reported by 21% on certolizumab and 11% on placebo. The corresponding incidence rate calculation demonstrated a lower incidence with certolizumab (294/1000 patient years) as compared to placebo (374/1000 patient years). Several infections were reported at a rate of at least 2% higher in the certolizumab group as was abdominal pain, arthralgia, anxiety, and rash. Injection site pain was more common in the placebo group.

- Serious adverse events / deaths / other significant events

The number of treatment emergent serious adverse events is given in the table.

Table 2.7.4:25 Number (%) of Subjects with Severe Treatment-Emergent Adverse Events, ≥0.5% of Subjects in Any Treatment Group, by Preferred Term: Crohn's Disease Pooled Population

Preferred Term	Placebo (N=426)		CDP870 400 mg (N=1350)		All CDP870 Doses (N=1564)	
Any severe AE	67	(15.7%)	286	(21.2%)	337	(21.5%)
Crohn's disease	14	(3.3%)	90	(6.7%)	99	(6.3%)
Abdominal pain	14	(3.3%)	45	(3.3%)	53	(3.4%)
Headache	9	(2.1%)	15	(1.1%)	21	(1.3%)
Perianal abscess	0		13	(1.0%)	14	(0.9%)
Intestinal obstruction	2	(0.5%)	11	(0.8%)	12	(0.8%)
Small intestinal obstruction	0		10	(0.7%)	10	(0.6%)
Abdominal abscess	0		7	(0.5%)	7	(0.4%)
Diarrhoea	5	(1.2%)	5	(0.4%)	8	(0.5%)
Fatigue	4	(0.9%)	5	(0.4%)	8	(0.5%)
Arthralgia	1	(0.2%)	6	(0.4%)	8	(0.5%)

Preferred Term	Placebo (N=426)		CDP870 400 mg (N=1350)		All CDP870 Doses (N=1564)	
Vomiting	1	(0.2%)	6	(0.4%)	8	(0.5%)
Influenza	0		6	(0.4%)	8	(0.5%)
Injection site pain	5	(1.2%)	4	(0.3%)	4	(0.3%)
Anaemia	2	(0.5%)	4	(0.3%)	4	(0.3%)
Pyrexia	2	(0.5%)	3	(0.2%)	6	(0.4%)
Nausea	4	(0.9%)	2	(0.1%)	5	(0.3%)
Sinusitis	2	(0.5%)	2	(0.1%)	3	(0.2%)
Groin pain	2	(0.5%)	2	(0.1%)	2	(0.1%)
Depression	2	(0.5%)	1	(0.1%)	2	(0.1%)
Dysmenorrhoea	2	(0.5%)	0		0	

AE=adverse event; CDP870 = certolizumab pegol
Note: Data displayed as number of subjects (% of subjects).
A subject experiencing more than one AE in a category is counted only once in that category.
Maximum severity is presented.
Source: ISS Table 8.1.5 Module 5, Section 5.3.5.3.3.2

There were no deaths in healthy volunteers or compassionate use program up to the cut-off date. Comparisons were based on estimated exposure in patient years – thus found to be 11-fold longer for certolizumab.

There were 11 deaths in the Crohn's disease studies, all in patients receiving certolizumab with an incidence of 11/1630 = 6 per 1,000. Eight of these deaths ere considered unrelated or unlikely related to treatment and two deaths occurred more than 12 weeks after study participation.

Infections

Serious adverse events due to infections were reported by 8% of patients treated with certolizumab as compared to 1% of those given placebo. Due to the longer exposure to certolizumab the incidence rate was 52 per 1000 patient years for placebo and 73 for certolizumab, and the relative risk associated with certolizumab was 1.4. There were four fatal infectious events, all associated with certolizumab treatment. These were due to pneumonias, sepsis and in one case a pneumocystis infection.

The frequency of sepsis, bacteraemia and viraemia was 0.5% and 0.4% in RA and CD for subjects exposed to certolizumab as compared to 0.2% for placebo, whereas the calculated incidence rates were slightly higher in the placebo groups.

The incidence rate for tuberculosis was 5/1000 patient years in CD and 7/1000 in RA Tuberculosis was reported in the certolizumab group only. One quarter of these infections were disseminated but there were no fatalities. Median time to onset of tuberculosis was 263 days, and three cases developed more than 220 days after the last certolizumab administration.

Gastrointestinal complications

The absolute percentage of subjects experiencing intestinal abscess (3.5% vs. 1.1%) and each of the other selected categories of serious gastrointestinal complications of Crohn's disease (exacerbation [9.3% vs. 4.7%], intestinal obstruction-stenosis-ileus [2.9% vs. 0.9%], perforation [0.2% vs. 0.0%], bleeding [0.3% vs. 0.0%], fistula [0.5% vs. 0.2%] and cancer [0.3% vs. 0.0%]) is higher on certolizumab than on placebo. Some patients reported the same event repeatedly. Taking relative duration of exposure into account, the incidence rate of serious adverse events of Crohn's disease exacerbation and intestinal fistula were lower on certolizumab than placebo, while the incidence rate of the other categories of complications (intestinal abscess [44.2 vs. 35.2 per 1,000 Patient-Years], obstruction/stenosis/ileus [36.3 vs 28.2 per 1,000 Patient-Years], perforation [2.9 vs 0 per 1,000 Patient-Years] , bleeding [3.6 vs. 0 per 1,000 Patient-Years] and cancer [36.3 vs 0 per 1000 Patient-Years]) were higher on active drug than placebo.

Cardiovascular events

Crohn's disease, rheumatoid arthritis and the global safety databases were searched. One of four serious adverse events related to cardiac ischemia in the placebo group died in comparison with 10 of 35 in the certolizumab group. The events occurred on average 386 days after start of treatment with certolizumab and 54 days after start of placebo. The majority of patients had strong predispositions and rheumatoid arthritis, and the majority of cases were rated as unrelated to trial treatment. The calculated incidence rates (events per 1000 Patient-Years) were slightly higher in the placebo group: 8/1000 PY (active) vs. 10/1,000 PY (placebo). Cardiac failure was reported in 9 subjects on certolizumab of which 3 were fatal, and there were no events in placebo.

Malignancies
Reports of skin papillomas were reported in patients given certolizumab only (5 events in pooled analysis) and a relationship with treatment could not be ruled out.

Other malignancies were reported for 39 patients given certolizumab and three given placebo. Small intestine carcinoma –a rare tumour- was encountered in 3 patients receiving certolizumab.

Given the 11-fold longer duration of exposure to certolizumab there was a slightly higher incidence rate associated with certolizumab (0.95/1000) in comparison with placebo (0.78/1000).

- Laboratory findings

For subjects in the Crohn's Disease Population, mean and median values for major hematology parameters at baseline were comparable in the certolizumab pegol 400 mg and placebo groups.

Coagulation time prolonged is listed in the proposed SPC as an uncommon event. Serious adverse events related to prolonged clotting time occurred in 19 subjects on certolizumab as compared to none given placebo. In the placebo controlled phases of the RA and Crohn's disease programmes, there were 5 and 4 serious adverse events related to prolonged clotting time, which raises concern and need to be elucidated through further data analyses

- Safety in special populations

Certolizumab pegol has not been studied in the pediatric population. Limited safety and efficacy data are available for elderly subjects with CD but population PK analysis showed no effect of age. The proposed SPC advises caution when using certolizumab pegol in elderly (≥65 years) subjects.

Only limited data are provided on pregnancy (13 events). Due to its inhibition of TNF-α, certolizumab pegol administered during pregnancy could affect normal immune responses in the newborn.

- Discontinuation due to adverse events

Treatment emergent adverse events leading to withdrawal are summarised in the table. The figures may exceed the number of unique subjects (n=1277) because patients could participate in both controlled and uncontrolled trials. The rate of withdrawals was similar in placebo and certolizumab groups in the placebo controlled trials.

Table 2.7.4:40 Number (%) of Subjects with Treatment-Emergent Adverse Events Leading to Withdrawal, ≥0.5% of Subjects in Any Treatment Group, by Primary System Organ Class and Preferred Term, by Controlled and Uncontrolled Study Design: Crohn's Disease Phase 3 Pooled Population

Primary System Organ Class Preferred Term	Placebo (N=329)		CDP870 400 mg (N=1277)		CDP870 400 mg by study design			
					Controlled (N=759)		Uncontrolled (N=1201)	
Any AE leading to withdrawal	21	(6.4%)	301	(23.6%)	63	(8.3%)	241	(20.1%)
Blood and Lymphatic System Disorders	1	(0.3%)	8	(0.6%)	0		8	(0.7%)
Anaemia	0		7	(0.5%)	0		7	(0.6%)
Gastrointestinal Disorders	9	(2.7%)	208	(16.3%)	29	(3.8%)	180	(15.0%)
Adominal pain	1	(0.3%)	7	(0.5%)	2	(0.3%)	5	(0.4%)
Crohn's disease	7	(2.1%)	159	(12.5%)	19	(2.5%)	140	(11.7%)
Intestinal obstruction	0		9	(0.7%)	2	(0.3%)	7	(0.6%)
Perirectal abscess	0		6	(0.5%)	1	(0.1%)	5	(0.4%)
Small intestinal obstruction	0		7	(0.5%)	1	(0.1%)	6	(0.5%)
General Disorders and Administration Site Conditions	2	(0.6%)	15	(1.2%)	5	(0.7%)	10	(0.8%)
Pyrexia	0		6	(0.5%)	0		6	(0.5%)
Infections and Infestations	5	(1.5%)	50	(3.9%)	14	(1.8%)	36	(3.0%)
Abdominal abscess	0		7	(0.5%)	1	(0.1%)	6	(0.5%)
Herpes zoster	2	(0.6%)	1	(0.1%)	0		1	(0.1%)
Perianal abscess	1	(0.3%)	12	(0.9%)	3	(0.4%)	9	(0.7%)

AE=adverse event; CDP870 = certolizumab pegol
Note: Data displayed as number of subjects (% of subjects).
A subject experiencing more than one AE in a category is counted only once in that category.
Source: ISS Table 8.1:16, ISS Table 8.1:55 Module 5, Section 5.3.5.3.3.2

Withdrawal rates were high and infections leading to withdrawal and/or antibiotic treatment were more common in patients treated with certolizumab.

- Discussion on clinical safety

Overall the safety profile of certolizumab appeared largely comparable with that of other anti-TNFα agents, although an increased risk for bleeding events has not been identified as a class effect.

In analysing the data, caution is warranted. The incidence rates of each event type were compared for certolizumab and placebo both in relation to number of patients affected and to duration of exposure. The method of estimating a patient exposure incidence is acknowledged and substantiated as an attempt to overcome the vast difference in drug exposure. However, this method could overcompensate and actually eliminate differences which would otherwise appear evident.

Withdrawal rates were high and infections leading to withdrawal and/or antibiotic treatment were more common in patients treated with certolizumab. The findings of an increased risk of serious infectious (and other) complications when treating patients with Crohn's disease with certolizumab are worrisome.

In line with other anti-TNFα medicinal products, patients exposed to certolizumab have an increased risk of developing tuberculosis.

In addition, an increased risk for bleeding was encountered. There were higher numbers of SAEs reflecting bleeding events in both the RA and CD populations (4 and 5 cases compared with none in the placebo groups during the placebo controlled studies), which raises concern. It is suggested that this might be related to the PEG component.

Certolizumab may cause both cardiac ischemia and cardiac failure in predisposed patients. The fact that such events were rare among Crohn's disease patients in comparison with rheumatoid arthritis may partly reflect predisposition of the latter patient population and partly the fact that those included into the Crohn's disease studies were younger. An increased risk may be anticipated in clinical practice outside clinical trials.

As expected, there is a slight increase of the malignancy rate also when observed cases were related to duration of exposure. The applicant has summarised the malignancies from the clinical trials and compassionate use programs with cetrolizumab in Crohn's disease. When comparing to figures of incidence rates in the general population, the number of small intestinal cancers appears increased; a tumour form which is rare. Although the available data are limited and no firm conclusions can be drawn, this finding raises concern.

Deaths were reported more common among patients receiving certolizumab. The majority of these resulted from cardiac events and others resulted from serious infections. Further analysis revealed that a number of deaths were most probably related to massive immunosuppression.

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

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the information provided in the application demonstrated consistent batch-to-batch production of CIMZIA achieving a consistent quality for the drug substance and the drug product. The manufacturing processes for the drug substance, Certolizumab pegol and the drug product 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. In addition, the viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. However, a major concern regarding the control of product purity remains and needs to be sufficiently addressed in order to ensure that the quality of the to be marketed medicinal product will be comparable to product on which the marketing authorisation application is based on.

Non-clinical pharmacology and toxicology

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. There are no studies on the carcinogenic potential of certolizumab pegol. As regards reproductive potential adverse effects, pre-clinical reproductive studies of certolizumab pegol provided some support for lack of reproductive and developmental toxicity but they are insufficient for recommendations on the use in women of child bearing potential and in pregnancy. There is insufficient information on the excretion of certolizumab pegol in human or animal breast milk.

Efficacy

Induction therapy in the intended indication

This application contains one phase III study, CDP870-031, where the possibility to induce remission is investigated. In this study, Certolizumab pegol was statistically significantly better than placebo, but the magnitude of the effect is not convincing (+8-10% responders at week 6 and 26). Certolizumab induced neither a statistically nor a clinically relevant rate of remission at week 6. The rate of remission obtained at week 4 was significantly higher than that obtained with placebo but the effect was less than that obtained with infliximab and with the higher induction dose of adalimumab. In Study CDP-032, the absolute difference between active treatment and placebo following induction treatment was, as expected larger, given the design of this trial. However, due to the initial open label design, it cannot provide information on the magnitude of the effect of induction therapy. These circumstances in combination, i.e. the small difference in relation to clinical response compared to placebo and the negative result for remission lead to the conclusion that efficacy with regard to induction treatment is insufficient.

Maintenance therapy in the intended indication

Considering maintenance treatment, the second phase-3 study, CDP870-032, provides support for an effect, as it demonstrates an effect of continued treatment in patients initially responding to open label induction therapy with CDP-870. In study CDP870-031, the results at week 26, as well as at week 6, showed an effect of active treatment in comparison with placebo. However, the rates of remission at week 6 and 26 in study CDP870-031 were not statistically significant. Efficacy was not affected by the initial CDAI score and not related to baseline CRP level, but was less in patients with more severe disease. The 26 week data can not be easily transformed into a treatment algorithm. Furthermore, the clinical relevance of the demonstrated efficacy has not been documented. A number of patients has not had a therapeutic attempt with steroids and/or immunosuppressants and were in fact treatment naïve when entered into the certolizumab pegol studies.

Moreover, there were no placebo controlled efficacy data beyond six months in either of the pivotal studies. Since the open trial data do not suffice to document long term efficacy, long term efficacy remains to be demonstrated. Controlled results for maintenance treatment over 12 months have been demanded and provided by the approved anti-TNF agents for this indication.

The long term data from study CDP870-033 were obtained in an open uncontrolled study. The dropout rate was high, and the data suggest a decline of the effect with time. Even though this study provides relevant safety data, efficacy can not be assessed.

Safety

Updated safety data with follow-up in a substantial number patients for at least one year identified several serious concerns. Overall the safety profile of certolizumab appeared in large compatible with that of other anti-TNFα agent. This relates in particular to a higher risk of serious infections, including gastrointestinal abscesses in the Crohn's disease population. Additional signals were a high rate of disease exacerbation, other complications to Crohn's disease and cardial events including deaths. Patients in study CDP870-032 were initially exposed to certolizumab, a fact which could question the validity of the global comparison of adverse events in the placebo controlled trials. In addition, there were no placebo controlled safety data beyond 6 months.

Certolizumab treatment was associated with an increased risk of intestinal obstruction and complications. Although a causal relation was not revealed it would appear that continued medical treatment when surgical intervention may have been indicated is one factor involved. The results indicate that more severe adverse events occur in the more ill patients. All deaths in Crohn's patients occurred in those treated with certolizumab and none in the placebo group. Impaired immune reaction could have been implicated in a few of the deaths of patients with rheumatoid arthritis. The applicant has summarised the malignancies from the clinical trials and compassionate use programs with cetrolizumab in Crohn's disease. When comparing to figures of incidence rates in the general population, the number of small intestinal cancers appears increased; a tumour form which is rare. Although the available data are limited, and no firm conclusions can be drawn, this finding raises concern. The higher number of SAEs reflecting bleeding events in both CD and RA populations (4 and 5 cases compared with none in the placebo groups during the placebo controlled studies) raises concern and needs to be elucidated through further data analyses.

- User consultation

A readability test (technical readability/traceability/comprehensibility/applicability) including scoring has been performed on the English version of the Patient Information Leaflet (PIL). It can be concluded that the present user test is not acceptable as it was not designed to achieve its goal to assess readability, to diagnose weaknesses and to make recommendations and enhance readability.

Risk-benefit assessment

The therapeutic effect is not considered clinically relevant, neither for induction or maintenance of remission, when put in relation to the safety profile of certolizumab. The risks associated with certolizumab treatment were substantial and contests the marginal efficacy on disease activity demonstrated in the pivotal studies. Safety issues in relation to an increased risk of bleeding remain unsolved. Furthermore, there are no controlled 12 month data to show sustained response beyond 6 months.

On the Quality part, major concerns regarding the control of product purity remain and need to be resolved in order to ensure that the quality of the to be marketed product will be comparable to product on which the marketing authorisation application is based on.

Therefore, the benefit/risk relation remains unfavourable for certolizumab pegol.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

Recommendation

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

the treatment of severe, active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant or who are intolerant to or have medical contraindications for such therapies

was unfavourable and therefore did not recommend the granting of the marketing authorisation for the following reasons:

- A major concern regarding the control of product purity and integrity remains. Specifications of the drug substance/product need to be set and the specification for the drug substance/product monomer needs to be tightened. Further all species resolved in the purity analysis should be identified;

- The results in study CDP870-031 have not demonstrated a clinically relevant effect with respect to induction treatment;
- The lack of 12 months controlled data on maintenance treatment;
- The safety profile of an anti-TNF agent, including the increased risk for infections as well as severe infections, and considerable uncertainties related to long-term safety, including increased risk for malignancy raise major concern. In addition, there is a signal of increased risk of serious events possibly suggestive of a prolongation in clotting time.

3 RE-EXAMINATION OF THE CHMP OPINION OF 15 NOVEMBER 2007

Following the CHMP conclusion that the risk/benefit balance of CIMZIA in the treatment of severe, active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant or who are intolerant to or have medical contraindications for such therapies, was unfavourable, the applicant submitted detailed grounds for the re-examination of the refusal.

The applicant presented a number of arguments regarding the grounds for refusal.

Ground for refusal 1:

- A major concern regarding the control of product purity and integrity remains. Specifications of the drug substance/product need to be set and the specification for the drug substance/product monomer needs to be tightened. Further all species resolved in the purity analysis should be identified.

Applicant's position:

Drug Substance and Drug Product Specifications
Based on the purity characteristics of the product used in clinical trials, the specifications are proposed to monitor and control purity of CDP870 Drug Substance and Drug Product routinely through four orthogonal approaches, all of which reflect clinical experience. Furthermore, the proposed limit for control of product monomer is tightened. In addition, all species resolved in the purity analysis are identified.

These specifications have therefore been set within sufficiently tight limits to ensure that the product intended for market will be entirely comparable in terms of purity criteria with batches used in clinical trials and, therefore, with the product as presented in the marketing authorization application. The applicant intends to continue to monitor the data on an on-going basis to ensure compatibility of specification with on-going manufacturing experience.

CHMP position:
For the assessment, data that were presented at the oral hearing at BWP meeting on 9 October 2007 and that were included in the applicant's application for re-examination were taken into account.

Drug Substance and Drug Product Specifications
The drug substance and drug product specifications have been set based on clinical trial batches. The proposed tests and limits are considered appropriate, and the data provided show a good batch to batch consistency of these attributes.

Identification of all species resolved in the purity assay

The applicant identified all species and clarified that the apparent discrepancy is based on an inherent baseline noise. The applicant's response is acceptable and correcting for this additional integration is necessary for estimation of purity.

Ground for refusal 2:

- The results in study CDP870-031 have not demonstrated a clinically relevant effect with respect to induction treatment.

Applicant's position:

The applicant argues that certolizumab pegol shows clinically relevant efficacy as induction treatment since:

- Results from CDP870-031 show that a statistically greater percentage of subjects respond to certolizumab pegol compared to placebo at week 6 and continued to respond at week 26.
- Clinically relevant effect on induction was demonstrated at early time points (weeks 2, 4, and 6) in CDP870-031 and CDP870-005.
- Results from CDP870-031 and CDP870-005 demonstrate a consistent treatment effect on induction of remission.
- The clinical relevance to induce remission in CDP870-005 and CDP870-031 shows similarity to results reported for adalimumab.
- In a subpopulation of subjects with severe disease, the treatment effect of certolizumab pegol to induce remission at week 6 and at earlier time points in CDP870-031 is clinically relevant.
- Supportive evidence on induction is provided from the open-label phase of CDP870-032.[1]

In more detail, the applicant states that the results from the two placebo-controlled studies, CDP870-005 and CDP870-031, have consistently shown that certolizumab pegol is an effective treatment in subjects with active Crohn's disease. The Phase III study, CDP870-031, is unique in that it was designed to evaluate the efficacy of certolizumab pegol through 26 weeks of continuous therapy. The study met its pre-defined co-primary endpoints which were to demonstrate a significant difference in the percentages of subjects in clinical response at Week 6 and at both weeks 6 and 26.

The study design of CDP870-031 allowed for assessment of certolizumab pegol as induction treatment because of the Week 6 time point. At week 6, 35.2% and 26.8% of subjects receiving certolizumab pegol and placebo, respectively, were in clinical response [OR=1.51 (1.08, 2.11) p=0.016]. The applicant assumed that the CHMP's questioning of the clinical relevance of the magnitude of the observed difference in remission between treatment groups might be due to comparison with results achieved with other TNF antagonists, and stated that this might not be appropriate since the study designs are not comparable. Comparisons were considered valid between certolizumab pegol and adalimumab when referring to studies CDP870-005/CPD870-031 and CLASSIC-I, respectively, and similarity with regard to remission at week 4 was claimed.

In addition, support for certolizumab pegol to induce response is provided from CDP870-032, where 428/668 (64.1%) of subjects responded to open-label certolizumab pegol. Response to open-label 400 mg certolizumab pegol induction therapy in the study population was claimed to be consistent with data reported for 5 mg infliximab in ACCENT I (58%) and 80/40 mg adalimumab in CHARM (58%), supporting clinical relevance of certolizumab pegol as induction therapy.

Finally, analyses of response and remission in subpopulations of subjects by disease severity show that subjects with severe disease consistently experienced benefit from certolizumab pegol induction therapy. In all analyses, a greater percentage of subjects receiving certolizumab pegol had response or remission compared to placebo during the induction period. The treatment effect for response and remission was particularly notable in subjects with a Baseline CDAI score $\geq$ 335.

[1] In addition, new data from study CDP870-042 was presented, however the applicant and the assessors/experts were reminded that this was not admissible in the re-examination procedure.

The applicant concludes that available clinical data confirm the efficacy of certolizumab pegol to induce remission. The magnitude of the effect at week 4 in two placebo-controlled studies, CDP870-005 and CDP870-031, is comparable to other approved anti-TNF therapies and supports the conclusion that induction of remission seen in the two studies is clinically relevant. In addition, induction of remission has been demonstrated in subjects with severe Crohn's disease.

CHMP position:

In the pivotal study CDP870-031 the primary endpoint was defined as percentage of subjects with clinical response at Week 6 and at both Weeks 6 and 26 in the strata defined by CRP ≥10 mg/l at baseline, with response being defined as reduction in CDAI ≥ 100. It is acknowledged that in this study the response in patients with CRP ≥ 10 mg/l at week 6 is statistically significant with p = 0.037 as well as at weeks 6 + 26 with p = 0.045.

However, the applicant has chosen to focus its primary analysis 1/ on the response rate (instead of remission rate), and 2/ to a subgroup of patients with CRP≥ 10 mg/l at baseline. Even if the response rate can be regarded as having some value in clinical practice, it remains that the main goal of treatment in clinical practice is the achievement of remission, as currently recommended in the EU guideline.

In the pivotal study CDP-870-031 induction of remission is only a secondary endpoint. No statistical difference is observed over the placebo arm on this particularly relevant endpoint (neither in the subgroup of patients with CRP≥10 mg/l nor on the overall population). It should be noted that exploratory results in terms of remission at week 6 were provided in the phase II study CDP-870-005, but no statistically significant difference between CPZ and placebo was found. In addition, the restriction of the primary analysis to those patients having a CRP≥10 mg/l at baseline to select the most severe patients is not considered convincing since the specificity of this criterion is not established.

The results of the primary analysis (i.e. induction of response at week 6 and 6+26) are not regarded as convincing neither in term of effect size nor with regard to their consistency as explored using sensitivity analyses. The magnitude of the treatment response is around 10% in the subgroup of patients with CRP≥10 mg/l and even lower in the overall population. Moreover, the results only remains statistically significant when considering patients with missing data as non responders but they are no longer statistically significant when considering the observed data only (neither when best/worst case was applied even if recognized as the most conservative approach).

The applicant has provided several exploratory analyses particularly of CDP870-031 in an attempt to further substantiate the benefit of the drug and to allow for further comparisons also with other TNF antagonists. However, these analyses can in no way compensate for the limitations of the efficacy demonstration and could only serve for planning future confirmatory studies. Of note that the comparison of trial results for other anti-TNF agents has several caveats (different designs, study population etc), and particularly the analyses for a sub-group, made post-hoc, cannot be considered robust evidence and have to be interpreted together with other results.

The CHMP consulted an ad-hoc expert group to address the question whether the co-primary endpoint chosen by the applicant in the pivotal study CDP-870-031 is adequate for a proper assessment of the benefit of the proposed medicinal product. The experts concluded that the chosen co-primary endpoint was relevant but that nevertheless a statistical and clinically relevant difference over the placebo arm should have been demonstrated in term of induction of remission. Furthermore, the choice to restrict the population for assessment to those with CRP ≥ 10 mg/l was regarded as inappropriate since CRP – although a useful follow-up tool for predicting response – cannot be used to select patients in need of therapy.

Ground for refusal 3:

- The lack of 12 months controlled data on maintenance treatment.

Applicant's position:

The applicant acknowledged the deviation from the applicable EU guideline, which requires at least 12 months controlled data on maintenance of remission, and justified the lack of this data as follows:

- Clinically relevant maintenance of remission is demonstrated at 26 weeks (6 months) in the randomized withdrawal maintenance study, CDP870-032.
- Clinically relevant maintenance of remission at Week 26 was also demonstrated in the placebo-controlled treatment study, CDP870-031.
- Continuing effectiveness of certolizumab pegol treatment to maintain clinical remission to 52 weeks and beyond has been shown in subjects who completed the qualifying studies and continued to receive CZP in the open-label study CDP870-033.
- Available placebo-controlled studies with two anti-TNF agents, infliximab and adalimumab, show that loss of response occurs mainly in the first 6 months with minimal change in the treatment effect with an additional 6 month controlled period.
- Results from statistical modeling of data from CDP870-032 accurately predicts response and remission equivalent to that seen over 12 months of treatment.
- Response after a total of 52 weeks of certolizumab pegol treatment in subjects receiving certolizumab pegol across CDP870-031, CDP870-032 and CDP870-033 is similar to that reported for other approved anti-TNF therapies with continuing effectiveness of certolizumab pegol to maintain remission beyond 6 months.
- No impact on long-term response is seen from antibody formation to certolizumab pegol.

Overall the applicant states that long-term maintenance of remission was consistently demonstrated in two independent, rigorously designed, and well-controlled 26 week studies, CDP870-031 and CDP870-032. Additional analyses of subjects with severe disease demonstrated clinically relevant maintenance of remission in both studies. CDP870-032 reflects clinical practice and results translate into a treatment algorithm for physicians to continue maintenance treatment in patients who respond to the open-label induction regimen.

Although the program did not include a placebo-controlled 12-month maintenance study, results from the certolizumab pegol program and the similarity in mechanism of action to other anti-TNF therapies provide, in the opinion of the applicant, adequate justification for this deviation from the guideline. The design of the entire program is scientifically sound and generated robust clinically relevant long-term safety and efficacy data. Twelve-month placebo- controlled studies evaluating infliximab and adalimumab show that the majority of relapses occur within the first 6 months and that the magnitude of effect between the anti-TNF therapy and placebo was similar at 6 and 12 months. These results support the conclusion that studies of 6 months duration provide adequate data to demonstrate the efficacy of anti-TNF therapy to maintain remission. Safety and efficacy results from CDP870-033 demonstrate that subjects receiving open-label certolizumab pegol through 12 months continue to maintain remission similar to subjects treated with approved anti-TNF therapies. Analysis of antibody formation with continued treatment in subjects in CDP870-033 shows that subjects have low risk for immunogenicity from prolonged exposure up to 18 months; overall the available data show that the frequency of antibody formation remains constant from week 18 to week 52, and the number of subjects developing antibody to certolizumab pegol is low and there is no indication of lower response in subjects who were antibody positive compared to antibody negative.

The applicant argues that the existing knowledge from available 12 month placebo-controlled studies of other anti-TNF therapies, the comparability of their 6 month results with the 6 month placebo-controlled study results from CZP, and their 12 month results with the open-label continuation studies of CZP covering a period up to 80 weeks, demonstrate the safety and efficacy of certolizumab pegol as long-term maintenance therapy for subjects with Crohn's disease.

CHMP position:

A critical limitation of the clinical development programme is that neither the pivotal study CDP-870-031 nor the maintenance study CDP-870-032 were designed to assess the maintenance of remission at a minimum of 12 months as requested in the applicable EU guideline.

The attempts made by the applicant to provide reassurance on the maintenance effect of certolizumab pegol are hampered with particular methodological limitations. In principle, the applicant claims maintenance of remission on the basis of the 26 weeks analysis from the pivotal study CDP-870-031, which is not regarded acceptable. It should be taken into account that maintenance of remission needs to be assessed in patients having previously achieved a remission, which corresponds to the 6+26 weeks analysis; however the pivotal study CDP-870-031 failed to demonstrate any statistical difference over the placebo in terms of remission at this time point.

The applicant's prediction of the maintenance beyond 26 weeks is based on a model of questionable validity. This model, aiming to predict the probability of remission up to 52 weeks, has been built on the basis of the study results derived from the open label study CDP870-032. According to the applicant, a temporal model was identified, that provided "an excellent" fit to the observed data through 6 months. However, data provided do not allow assessing the validity of the computed model. Moreover, still according to the applicant, the observed data used to validate the model built were the data derived from the open label non comparative study CDP870-033. However, it is noteworthy that if this study could provide data beyond 26 weeks with certolizumab pegol, the same does not hold true for the validation of the estimation made for the placebo arm at similar endpoint.

The historical comparison is intrinsically flawed by critical limitations. Comparison with long-term studies with other anti-TNF agents is hampered by many factors. The results cannot be compared with the results from Study CDP-870-032 that assessed maintenance of efficacy only in patients responding to certolizumab pegol. Comparisons with Study CDP-870-031 are more showing in a trend towards a inferiority of certolizumab pegol. Thus, the data from the open-label non comparative extension study CDP-870-033 are difficult to interpret for several reasons and overall the data presented do not provide any robust evidence for long-term efficacy of certolizumab pegol. Moreover, a decrease in concomitant doses of corticosteroids and even a steroid free remission was observed with other TNF antagonists which is of major importance in clinical practice. This is not the case for the certolizumab pegol.

At present no major issue has been raised on the development of anti-CDP870 antibody although a trend for a lower efficacy is observed in patients having developed anti-CDP870. This issue would need further investigation.

The Ad-hoc Expert group, when consulted by the CHMP, stated that maintenance of remission should have been convincingly demonstrated at one year.

Ground for refusal 4:

- The safety profile of an anti-TNF agent, including the increased risk for infections as well as severe infections, and considerable uncertainties related to long-term safety, including increased risk for malignancy raise major concern. In addition, there is a signal of increased risk of serious events possibly suggestive of a prolongation in clotting time.

Bleedings and coagulation parameters

Applicant's position:

The applicant presented a review of all potential bleeding events from the clinical development programmes in Crohn's Disease and Rheumatoid Arthritis, respectively, in order to assess whether treatment with certolizumab pegol is associated with a bleeding safety signal. Coagulation tests were only performed during some of the studies in the Rheumatoid Arthritis clinical program but not during

clinical studies in Crohn's Disease. Extensive testing of the effect of certolizumab pegol or its components (Fab′, or PEG) on coagulation assays was performed by independent experts.

The review of all TEAE and serious bleeding events in the Crohn's Disease programme showed no evidence for increased bleeding risk. Overall, there were 17 reports of serious bleeding events among 2166 subjects who received certolizumab pegol for more than 2100 pt-yrs in controlled and open-label studies. The incidence of bleeding events was similar between certolizumab pegol and placebo and there were only 2 serious bleeding events in certolizumab pegol-treated subjects during the controlled phases of the clinical studies. The types of bleeding events reported were consistent with those expected in subjects with Crohn's disease or could be attributed to underlying CD/GU conditions.

The respective review of all TEAEs and serious bleeding events in the Rheumatoid Arthritis programme also showed no evidence of increased bleeding risk. When taking into account differences in exposure to certolizumab pegol and placebo, the rate of all bleeding events was similar. There was no increase rate of bleeding events with greater exposure. The most frequent events involved the GU tract (blood in urine and dysfunctional uterine bleeding) or related to injection of drug (bruising and ecchymosis). The majority of serious bleeding events also involved the GU tract. All serious bleeding events were extensively reviewed and were attributable to underlying conditions.

With regard to the available data from coagulation tests, the review of the clinical data shows no association between bleeding and reports of abnormal coagulation assays. In RA and healthy volunteer studies, increases in the aPTT were only seen when aPTT was assayed using the specific kits Hemosil aPTT-SP and Stago PTTLA. Subsequent investigations have shown that the aPTT prolongation in these assay kits is due to in vitro assay interference and not due to in vivo disruption of coagulation activity.

From a nonclinical viewpoint, elevations in PT and aPTT with certolizumab pegol were noted during conduct of preclinical studies. In all preclinical studies, no adverse bleeding or clotting related events were associated with abnormalities in PT and aPTT lab results with doses up to 100mg/kg/week (50 times the maximum human recommended dose). Importantly, no findings of occult bleeding were found on necropsy. These laboratory abnormalities did not occur in all animal studies and subsequent investigations showed that certolizumab pegol and PEG interfere with the phospholipid component in some assay kits.

The conclusion from in vitro assay interference studies is that certolizumab pegol or PEG interferes with some commercial assays to measure aPTT, including the Hemosil aPTT-SP and Stago PTTLA assays used in the clinical studies. The effect is related to interference by certolizumab pegol and PEG with the phospholipid component of the assays. The interference is an in vitro phenomenon and there is no evidence for an effect on in vivo coagulation function. A draft wording for section 4.4 of the SmPC was suggested together with a reflection in the Risk Management Plan.

CHMP position:

With regard to the data from the studies in Crohn's Disease, it is recognized that the proportion of patients experiencing bleeding events during placebo-controlled studies was similar among placebo-treated patients and certolizumab pegol-treated patients (4.5% in each treatment arm). However, regarding the type of bleeding events reported in each treatment arm, different trends were observed that need to be highlighted: while bleeding events may be mostly related to the underlying CD disease among placebo-treated patients (blood in stool 1.9%, anal haemorrhage 0.7%) or related to the injection itself (injection site bruising 0.9%) patients treated with certolizumab pegol experienced other kind of bleeding events, not or less observed in the placebo arm such as blood in urine (0.8%), conjunctival haemorrhage in one patient (0.1%), epistaxis (0.3%) and dysfunctional uterine bleeding (0.3%). These data seem to be confirmed by safety data derived from all certolizumab pegol doses studies (N=1564) where similar trends were observed: blood in urine was reported in 1.3% of certolizumab pegol-treated patients (n=20), conjunctival haemorrhage were reported in 4 patients (0.3%), epistaxis were observed in 11 patients (0.7%) and dysfunction uterine bleeding were reported

in 12 patients (0.8%). Of note, two cases of periorbital haematoma were also reported in all certolizumab pegol studies.

The applicant also argues that the higher incidence of bleeding events in all studies group (8.9%) compared to the certolizumab pegol-treated subjects in the placebo-controlled studies (4.5%) is due to the 3-fold increase in exposure (1200 patient-years versus 422 patient years). This difference in the duration of exposure between placebo-controlled studies and all studies group is acknowledged and has indeed to be taken into account in the assessment of safety data. However, in spite of that, it deserves to be noted that the incidence of conjunctival haemorrhage is estimated to be 0.2 for 100 patient-years in certolizumab pegol-treated patients in all placebo-controlled studies and to 0.3 for 100 patients-years in certolizumab pegol-treated patients in all open-label studies group. Moreover, the incidence of dysfunctional uterine bleeding slightly increased in certolizumab pegol-treated patients in All studies group (incidence of 1 /100 patient-years) compared to the one in certolizumab pegol-treated patients from placebo-controlled studies (0.7/100 patient-years).

Safety data on bleeding events in the Rheumatoid arthritis studies slightly differ to those reported in Crohn's disease studies. In particular, no increased risk of blood in urine or conjunctival haemorrhage is retrieved between placebo-treated patients and certolizumab pegol-treated patients. However, a slight difference still persist in the incidence of dysfunctional uterine bleeding events between certolizumab pegol-treated patients and placebo-treated patients, even though no increase in these events occurred with long-term exposure to certolizumab pegol in the open-label studies.

The available data did not show a clear association between bleeding events and abnormal coagulation parameters. Based on the data provided by the applicant it seems that there is an in vitro interference between CZP and phospholipid contained in some assays kits used to measure aPTT values. A direct effect of CZP on the coagulation activity is not apparent. It would however be important to clarify in the SmPC which test kits are expected to interfere with the measurement of aPTT levels.

Moreover, although available data suggest an in vitro interference between certolizumab pegol and some coagulation assay and although no clear association was retrieved between bleeding events and coagulation abnormalities, a higher incidence of some type of bleeding events (mainly dysfunction uterine bleeding events and conjunctival haemorrhage) occurred in certolizumab pegol-treated patients included in Crohn's disease studies. In that point, the applicant's position that the bleeding events were typical for the subject populations studied is not supported. Moreover, this type of events has not been described with other anti-TNF agents.

Other adverse events of special interest

Applicant's position:

The Applicant provided a comprehensive review of serious adverse events (SAEs) for all events of special interest (deaths, malignancies, opportunistic infections, tuberculosis, malignancies, serious hematological events, and events associated with increased bleeding) from the development programmes in the indications Crohn's Disease, Rheumatoid Arthritis, and Psoriasis (cut-off date 16 July 2007). This review showed that the safety profile of certolizumab pegol is similar to that of other anti-TNF agents. Like other anti-TNF agents, there is an increased risk for infections including serious infection with certolizumab pegol. The type and severity of infections are those commonly reported with other anti-TNF agents and can be managed successfully medically. Other potential risks with anti-TNF therapies include malignancy as well as demyelinating disorders, lupus-like reactions, and exacerbation of heart failure. Review of safety data shows no increased risk for these events with certolizumab pegol in the clinical studies. The applicant did commit to further assessment of these safety events in the Risk Management Plan.

CHMP position:

Based on the available data it can be concluded that in general, the safety profile for certolizumab pegol – except for the risk for bleeding (see above) - is probably similar to other anti-TNF agents, but

safety evaluation in Crohn's Disease patients is to some extent hampered by the lack of long-term controlled data. Due to the design of the Crohn's Disease studies, it appears that the overall number of patients that have received placebo only for more than 6 weeks is low, making interpretation of data with regard to long-term safety even more difficult. However, serious and opportunistic infections occurred with certolizumab pegol, including tuberculosis, typical class AEs for an anti-TNF agent and thus it can be concluded that certolizumab pegol is associated with the same risks as others of the same class.

The CHMP consulted the Ad-hoc Expert group with regard to the safety profile of certolizumab pegol. The experts considered the compound as having a similar safety profile to that of medicinal products of the same class and the safety issues to be manageable with particular monitoring recommended in the SPC. For the risk of bleeding outside GI tract the experts indicated that the clinical specialist can handle these in daily practice. The spurious event of prolonged aPTT due to interference of certolizumab pegol with the *in vitro* test kit was recognised as well.

Overall conclusion on grounds for re-examination

Quality aspects

The applicant has adequately addressed the control of product purity and integrity. Specifications of the drug substance and drug product have been set and the specifications for the drug substance and drug product have been tightened. Furthermore, all species resolved in the purity analysis have been identified. Sufficient assurance has been given that the quality of the to-be-marketed medicinal product will be comparable to the product on which the marketing authorisation application is based on. From a Quality point of view, the application for marketing authorisation for Cimzia is approvable.

Efficacy aspects

In the pivotal study CDP870-031, the applicant has chosen to focus its primary analysis to the response rate (and not to the remission rate). Even if the response rate can be regarded as having some value in clinical practice, it remains that the main goal of treatment in clinical practice is the more ambitious achievement of remission, as currently recommended in the EU guideline. The study has failed to demonstrate any statistical difference over the placebo in the more clinically meaningful endpoint of induction of remission (primary endpoint recommended in the EU guideline).

When now focusing on the primary analysis chosen by the applicant (i.e. induction of response at week 6 and 6+26), the results cannot be regarded as convincing neither in term of effect size (around 10%) nor on their consistency through the sensitivity analyses performed.

As an additional critical limitation of the clinical demonstration the maintenance of the effect is not even captured beyond 26 weeks. According to the EU guideline maintenance of remission should be demonstrated over 52 weeks. This has been demonstrated for other anti-TNFs agents.

In its response the applicant has made several attempts to add robustness to the demonstration of efficacy. However, these attempts mainly consist of exploratory post-hoc analyses and can not be regarded as an acceptable way to support a marketing authorisation. All the more they can be useful to capture an exploratory subgroup where the effect size of the drug would be particularly noticeable and would worth being focused on, in a subsequent confirmatory study.

Safety aspects

The general safety profile for certolizumab pegol is considered similar to other anti-TNF agents; however safety evaluation in Crohn's disease patients is to some extent hampered by the lack of long-term controlled data. Due to the design of the Crohn's disease studies, it appears that the overall number of patients that have received placebo only for more than 6 weeks is low, making interpretation of data with regard to long-term safety even more difficult. However, serious and opportunistic infections occurred with certolizumab, including tuberculosis, typical class AEs for an

anti-TNF agent and thus it can be concluded that certolizumab is associated with the same risks as others of the same class.

It needs to be recognised though that in contrast to the other anti-TNFα agents a potential higher risk of bleeding events was observed in certolizumab pegol treated patients when considering all available safety data for certolizumab pegol, which comprises studies in Crohn's disease and Rheumatoid arthritis. Clinical data from placebo controlled studies in Crohn's disease did not show an increase in the rate of bleeding adverse events with certolizumab pegol when compared to placebo, although some type of bleeding events observed in certolizumab pegol–treated patients were not necessarily typical of the populations studied (mainly dysfunction uterine bleeding, conjunctival haemorrhage, epistaxis). When referring to all studies in Crohn's Disease (i.e. including not placebo controlled studies), there was an increased rate of bleedings in the group of patients that had received certolizumab pegol compared with the rate in patients receiving certolizumab pegol in placebo controlled trials, however longer exposure times in the overall patient group might explain this difference. Also, results from Rheumatoid arthritis studies indicate that there might be an increased risk of bleeding, although the difference compared with placebo was only minimal when corrected for exposure time.

The role of certolizumab pegol and the mechanism behind these bleeding events remain unclear. Even though bleeding events may potentially represent an additional signal to a safety profile already judged as particularly worrying as for all anti-TNFs agents, they are nevertheless, per se, not perceived as a major issue (serious bleedings were not commonly reported; apart from interference with clotting times, relation with the drug not clearly established).

Convincing data demonstrated that certolizumab pegol interferes with many of the commercially available kits for testing APTT, with prolongation of APTT up to 40%. This interference is most certainly related to the PEG fraction of the active substance. The effects of PEG on various proteins is not a new phenomenon and rarely is it related to specific binding to the proteins, rather they change the protein surroundings, such as lipophilic environment, prevent binding of blood proteins to plastic containers etc. Interference was addressed in the proposed SmPC and proposed RMP.

Benefit/risk assessment

The available clinical data does not demonstrate that certolizumab pegol has a clinically relevant effect in the claimed therapeutic indication, neither for induction or maintenance of remission. The safety profile of certolizumab pegol covers the risks associated with anti-TNF agents in general and leaves some uncertainties regarding the potential risk for bleedings since an association of certolizumab pegol with the occurrence of the bleedings cannot be ruled out; the latter will need further investigation.

These risks together with a not sufficiently demonstrated clinical efficacy lead to the assessment that the benefit/risk relation remains unfavourable for certolizumab pegol.

CHMP conclusion on benefit/risk

Having considered the grounds for the re-examination from the applicant, the discussion during the Ad-Hoc Expert Group meeting and the CHMP members' discussion during the oral explanation, the CHMP is of the opinion that the benefit/risk for CIMZIA in the claimed indication remains negative.

Grounds for refusal

- The results in study CDP870-031 have not demonstrated a statistically and clinically relevant effect with respect to induction treatment;
- The lack of 12 months controlled data on maintenance treatment;
- In the light of the limited evidence of efficacy and the safety concerns with CIMZIA, also in view of the known safety profile as an anti-TNF agent, the benefit risk is negative.